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Working Memory Late Effects in Survivors of Pediatric Acute Lymphoblastic Leukemia

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Working Memory Late Effects in Survivors of Pediatric Acute Lymphoblastic Leukemia

by

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Dedication

I would like to dedicate this project to the patient to which I had the pleasure of first providing a neuropsychological assessment. She is a happy, healthy survivor of Acute Lymphoblastic Leukemia. She piqued my interest in this topic and it has lead to a beautiful and fruitful career focus. I thank you!

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Working Memory Late Effects in Survivors of

Pediatric Acute Lymphoblastic Leukemia

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Acute Lymphoblastic Leukemia (ALL) is the most commonly diagnosed malignancy in children (Pui, 2000; Steen & Mirro, 2000; American Cancer Society, 2009; Westlake & Bertolone, 2002). Modern advances in cancer treatment, such as combination chemotherapy (Ettinger, Bond, & Sievers, 2002; Rodman & Reed, 2009), have increased survivorship of ALL to nearly 85% (Westlake & Bertolone, 2002). This new population of ALL survivors is displaying a unique profile of cognitive late effects that are a result of the treatment (e.g. chemotherapy) which while effective in eradicating the disease, has neurotoxic properties (American Cancer Society, 2009). Late effects have been discovered in a variety of cognitive skills, including academic achievement, visual-

spatial skills, and processing speed, but the most commonly seen late effects are in the areas of attention and memory (e.g. Askins & Moore, 2008; Cullen, Derrickson, & Potter, 2002; Leigh, 2000). While working memory is a skill that depends on both attention and memory (Baddeley 2000) and is important in both academic performance and life skills (Dark & Benbow, 1991; Geary, Hoard, & Hamson, 1999), it is relatively unstudied in this population.

The purpose of this study was to investigate working memory abilities in survivors of pediatric ALL. Working memory skills in this population were compared to both sample and population IQ. Comparisons of verbal and nonverbal working memory and male and female working memory skills were compared as well. First, working memory, as measured by a composite, was not found to be significantly impaired when compared to sample and population mean IQ. However, a single subtest, Digit Span Backward from the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV; Wechsler, 2003), when compared to IQ outside the composite, was found to be significantly below IQ for both the sample and population mean. Second, no gender differences were found for working memory abilities. Finally, there was no difference between nonverbal and verbal working memory performance. While the results were nonsignificant, verbal working memory was worse than nonverbal working memory, which was the opposite of the hypothesized pattern. Implications, recommendations, and limitations of this study are discussed in detail.

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Chapter I: Introduction

Cancer is the leading cause of death in children under the age of 15 (National Childhood Cancer Foundation, 2009). Among the cancers diagnosed each year, Acute Lymphoblastic Leukemia (ALL) is the most commonly diagnosed, affecting roughly one per thousand children (American Cancer Society, 2009). Due to medical advances over the past 40 years, survival rates of ALL have increased from 15% to 85%, with over 90% of children diagnosed with ALL surviving five years post diagnosis (National Childhood Cancer Foundation, 2009). Treatment protocols including chemotherapy, tumor resection, radiation, and combinations of those methods have been researched, modified, and improved, resulting in dramatically higher rates of survival.

While the dramatically increased survival rates are benevolent, the methods used to treat these children may produce damaging side effects. Most current treatment protocols act directly on the Central Nervous System (CNS); chemotherapy to the CNS with methotrexates is currently the most common treatment protocol for newly diagnosed cases of ALL (Margolin, Steuber & Poplack, 2002; Moe, 2003). While methotrexates improve survival rates (Moe, 2003), it is highly neurotoxic. Thus, the treatment protocol for ALL, while highly effective in increasing survival rates, may be associated with cognitive decline for individuals who survive the disease.

Since the increased survival rate of those diagnosed with ALL is a product of more recent treatment protocols, literature investigating the abilities and well being of survivors with regard to modern treatment is limited. However, current research of

cognitive abilities in survivors of ALL has generated common particular cognitive vulnerabilities to treatment on the CNS. Children who have undergone neurotoxic treatments such as chemotherapy may be susceptible to developing long-term neurocognitive deficits which are commonly called *late effects*. The most common late effects seen in survivors of ALL negatively impact short term memory and attention processes (Jansen et al., 2008; Kingma, Dommelen, Mooyaart, Wilmink, Deelman & Kamps, 2001; Mountour-Proulx et al., 2004; Thompson et al., 2001). Other reported problems associated with late effects include math performance (Kaemingk, Carey, Moore, Herzer, & Hutter, 2004), nonverbal skills (Brown et al., 1998; Carey et al., 2006), and fine motor functioning (Jansen et al., 2008). Additionally, a diagnosis prior to age 5 correlates with more severe late effects (Copeland et al., 2001), and ALL is most often diagnosed before age 5.

Attention and short-term memory are extremely important cognitive processes that may affect other systems of cognitive functioning in individuals. Working memory, the ability to hold information in immediate attention, apply mental control, and manipulate the information (Floyd, 2003), involves both attention and memory. Working memory is involved in the cognitive processes used to execute both attention and auditory processing (Dark & Benbow, 1991; Geary, Hoard, & Hamson, 1999; Hale, Fiorello, Bertin, & Sherman, 2003; Knudsen, 2007; Sander & Poeppel, 2006). The most common theory of working memory has been developed by Baddeley and Hitch (1974), who outlined three components of working memory: the phonological loop (interprets and stores auditory information), the visuospatial sketchpad (interprets and stores visual

information), and the central executive (supervises and controls input and output of information). This theory of working memory, as well as the existence of its components, is well-supported by research (Baddeley & Hitch, 1994; Baddeley, Lewis, & Vallar, 1984; Bishop & Robson, 1989). In order for the working memory system to successfully manipulate information an individual must (1) attend to the information and (2) hold the information in short-term memory. Working memory is implied in the successful completion of many school and real life activities, such as note-taking, processing auditory directions, and performing mental calculations.

Given the components necessary to execute working memory processes and common late effects of children treated for ALL, it may be implied that working memory processes would be negatively affected by neurotoxic treatments such as chemotherapy and radiation. However, given the relatively brief history of the knowledge of late effects in children treated for ALL, this is an area that little research has been dedicated to.

The purpose of this study is to determine whether working memory is affected by neurotoxic CNS treatment protocols used on survivors of Acute Lymphoblastic Leukemia. Research has shown that treatment protocols for ALL have resulted in the decline of short-term memory and attention processes. Research has also shown that short-term memory and attention are integral to the working memory process. However, there is little research on whether working memory deficits are evident in survivors of ALL treated with chemotherapy and/or radiation.

Chapter II: Review of the Literature

A review of the literature in the areas of pediatric cancer and acute lymphoblastic leukemia (ALL), the treatment of ALL, late effects of treatment for ALL, and the cognitive skill of working memory will be presented. By critically analyzing the current research base in these areas, a foundation for conducting the present study will be established. The first section discusses pediatric cancer and its incidence, then acute lymphoblastic leukemia specifically, including its incidence and survival rates. Next, a detailed discussion of possible treatments for ALL, including chemotherapy, radiation, and transplants will be presented. Current treatment protocols for ALL will be presented here as well. The next section includes a description of late effects of cancer and a discussion of common late effects seen in survivors of ALL, including attention and memory deficits. Demographic and developmental considerations related to late effects will also be discussed in this section. The last section discusses the cognitive ability of working memory and its relation to various academic deficits.

Cancer

Cancer is a disease that begins when cells in an individual‟s body begin to grow out of control (American Cancer Society, 2009). In the United States, cancer is the second leading cause of death, and nearly half of all men and one third of all women will develop cancer during their lifetimes (American Cancer Society, 2009). Cancer affects both sexes, all racial and ethnic groups, as well as all ages and stages of development.

There are many different varieties of cancer, but each type begins due to uncontrolled growth of abnormal cells caused by a genetic mutation. In children, normal cells grow and divide at a rapid rate to allow for growth; as adults, cells grow and divide at a slower rate. Cancerous cells are different from both child and adult normal cells because not only do they grow and multiply at a quicker rate, but they also outlive normal cells (American Cancer Society, 2009). They can also invade healthy cells and turn them into cancerous cells (American Cancer Society, 2009). When cancer affects an individual, it may begin as a single cell and proceed to invade healthy cells, then multiply (Steen & Mirro, 200).While all cancers share this rapid growth and invasion pattern, the rates of growth differ between types and often require very different courses of treatment (American Cancer Society, 2009).

Incidence of Pediatric Cancer.

Among diseases that affect children and adolescents, cancer is the most common. Approximately 12,500 children and adolescents (or 1-2 children per 10,000) will develop some form of malignant cancer each year (National Childhood Cancer Foundation; Daly, Kral & Brown, 2008). It is also estimated that one in 350 American children will develop cancer before the age of 20 (Steen & Mirro, 2000). Cancer is the second leading cause of death in children ages 1 to 14 years, following accidents (Foley & Fergusson, 2002). Additionally, the incidence of cancer in children has been increasing slightly, but consistently, from year to year (Steen & Mirro, 2000).

There are many different types of cancer that affect the pediatric population, and certain types of cancer more commonly affect children than adults. In adults, cancer most commonly affects epithelial tissues, which is extremely rare in the pediatric population. In children, cancers most often arise from deep-seated tissue (e.g. bone marrow, central nervous system) which is less common in adulthood (Ruccione, 2002). Steen & Mirro (2000) report that leukemia, lymphoma, and Central Nervous System (CNS) cancers are the predominant types found in children and adolescents. Other common types of cancer found in children are CNS tumors (19% of diagnoses), Lymphomas (12%), Neuroblastomas (8%), Soft Tissue Sarcomas (6%), Genito-urinary Tumors (6%), Ostesarcomas (5%) and Retinoblastomas (2%; Steen & Mirro, 2000).

Leukemia.

Leukemia is a type of cancer that typically starts in the bone marrow and can spread to the blood, where it can travel to and infect various organs (American Cancer Society, 2009). Leukemia is different from many cancers in that it does not form tumors; instead, it circulates throughout the blood forming organs and eventually through the blood.

Various sources name leukemia as the most common type of cancer in the pediatric population (American Cancer Society, 2009; Pui, 2000; Steen & Mirro, 2000). Leukemias reportedly affect between 25 and 31 percent of children diagnosed with cancer (Steen & Mirro, 2000; Westlake & Bertolone, 2002). According to the American Cancer Society (2009), leukemia accounts for one third of all pediatric cancers. Leukemia

is more commonly found in children than adults as there is a peak in diagnosis between ages 2 and 5 years (Pui, 2000).

Onset of leukemia is usually sudden. A child with leukemia will usually seek medical attention with the complaint of fever, sometimes accompanied by fatigue (Pui, 2000). Some children will also present with bone or joint pain, headache, vomiting, weight loss, and other symptoms. It should be noted that these symptoms may accompany a variety of different pediatric illnesses (flu, cold, infection) and these illnesses must be ruled out before leukemia can be diagnosed. When the individual‟s symptoms are not accounted for by another childhood illness, the patient is referred to a hemotology/oncology specialist. Once an individual is seen by a hematologist/oncologist, the diagnosis of leukemia can be confirmed. The exam usually includes workups in various systems, including blood, urine, and bone marrow analysis. The diagnosis of leukemia can be confirmed by the presence of leukemic cells in the bone marrow. Bone marrow in a patient with leukemia typically filled with leukemic lymphoblasts (lymphoblast cells affected and changed by leukemia; Pui, 2000). Once a diagnosis of leukemia has been confirmed, the patient often immediately begins induction chemotherapy (discussed later), and the initial symptoms (e.g. fever, bone pain) will subside in one to three days (Pui, 2000).

There are several types of leukemia: Acute Lymphoblastic Leukemia (ALL), Acute Myelogenous Leukemia (AML), and Hybrid Leukemia. ALL, the most common of the leukemias, begins in lympoid cells in the bone marrow. AML originates in the cells

that form white blood cells, red blood cells, or platelets. Hybrid leukemias have features of both ALL and AML, and these cases are extremely rare (American Cancer Society, 2009).

Acute Lymphoblastic Leukemia (ALL).

Among leukemias, the most common type is Acute Lymphoblastic Leukemia (ALL; American Cancer Society, 2009; Pui, 2000; Steen & Mirro, 2000; Westlake & Bertolone, 2002). ALL is commonly referred to as the most common malignancy diagnosed in the pediatric population. ALL reportedly accounts for 70 percent of cases of leukemia in individuals ages 19 and younger, and 25% of all pediatric cancers (Westlake & Bertolone, 2002). As with other leukemias, the typical age of onset is between 2 and 5 years. The frequency of ALL varies in different geographic and ethnic groups. Caucasian children are most likely to be affected by ALL and black children are least likely to be affected world-wide (Pui, 2000). Countries vary in the percentage of children affected by ALL, and the general consensus is that more industrialized countries have a higher incidence of ALL due to both environmental (underdiagnosis in developing countries, varied exposure to infections, death from other causes) and genetic factors (e.g. Down Syndrome; Westlake & Bertolone, 2002). Additionally, males are more likely than females to have a diagnosis of ALL (Pui, 2000).

Survival Rates of ALL.

Due to vast improvements in treatment protocols, the survival rates of ALL have dramatically improved over the last few decades. 50 years ago, if a child was diagnosed

with ALL, he or she was likely to die, usually within a period of months. In 1963, the survival rate of childhood cancer (5 years post diagnosis) was 28%; thirty years later, the survival rate was 72% (Steen & Mirro, 2000). Currently, over 80% of children diagnosed with ALL will survive at least 5 years post diagnosis (Westlake & Bertolone, 2002). Recent survival rates are reported to be between 72 and 95% for children diagnosed with ALL. As medical technologies continue to advance and the knowledge of the efficacy of various treatments increases, it is expected that survival rates will continue to climb. In 1999, less than 3 in 100,000 people ages 15 and younger died from cancer (Steen & Mirro, 2000).

Treatment of ALL

Over the last few decades, the treatment of ALL has gone through various iterations, leading to the present, in which 80% of children diagnosed with ALL survive at least 5 years post diagnosis. This dramatic increase is due to the increase in medical knowledge of the disease, its course, individual factors, and improvement in medical technologies. Currently, an individual diagnosed with ALL may receive treatment in the form of chemotherapy, radiation, bone marrow or stem cell transplants, or any combination of these treatments.

Chemotherapy.

Chemotherapy refers to the use of drugs to kill cancer cells (American Cancer Society, 2009; Rodman & Reed, 2009). The drugs used in chemotherapy may enter the system in a variety of ways, including injection into the vein, injection into cerebrospinal

fluid, or consumed in capsule form. When treating ALL with chemotherapy, either alone or in conjunction with other treatments, it is common to use a combination of drugs instead of a single drug (Rodman & Reed, 2009). This is called combination chemotherapy, and certain combinations are implicated when treating specific cancers (Ettinger et al., 2002). Using drugs in combination has several advantages. First, the combination of drugs is preferred because individual cancer cells in ALL may have more than one abnormality or there may be several different types of cancer cells in an individual with ALL. Specific drugs are indicated to target certain abnormalities, which is why multiple drugs are often used to ensure that each of the abnormalities is eradicated. Second, the use of multiple drugs in an individual can be beneficial in that cancer cells have the capability to become resistant to drugs. Cancer cells may mutate or evolve over time, thus making them immune to particular drugs. By using a combination of drugs in chemotherapy, it reduces the likelihood that the drugs will become ineffective due to evolution of cancer cells in an individual (Rodman & Reed, 2009). Third, clinical studies have shown that certain drugs in combination show an enhanced effect when working together as compared to separate administrations (Ettinger et al., 2002). Thus, using specified chemotherapy drugs in combination increases efficacy of treatment. Common drugs used in chemotherapy include vincristine, methotrexates, prednisone, mercaptopurnine, and hydrocortisone (Cheok & Evans, 2009).

Chemotherapy is a very popular treatment in individuals diagnosed with ALL as 80% of patients with ALL can survive with chemotherapy alone (Pui, 2000). There are three phases of chemotherapy that are administered to all patients undergoing chemo

treatment: Induction, Consolidation, and Maintenance (American Cancer Society, 2009). The entire course of chemotherapy treatment usually lasts between two and three years.

Induction is the first phase of chemotherapy. Its purpose is to quickly enter the system and destroy as many cancer cells in the least possible amount of time (American Cancer Society, 2009). In children with ALL, this is accomplished by injecting chemotherapy directly into the cerebro-spinal fluid (CSF) to prevent the cancer from spreading to the central nervous system (CNS). This method of delivery is called intrathecal chemotherapy and the drugs are often injected directly to the spine via lumbar puncture (American Cancer Society, 2009). The induction phase is complete once more that 99.9% of cancer cells have been destroyed. Once the induction phase is complete, the patient is considered to be in remission, and more that 95% of children diagnosed with ALL will enter remission after 1 month of induction chemotherapy (American Cancer Society, 2009).

The consolidation phase follows remission after the induction phase. The purpose of consolidation is to destroy the remaining cancer cells. The consolidation phase uses combination chemotherapy as well, and common drugs administered include cyclophosphamide, cytarabine, methotredate, and asparaginase (Westlake & Bertolone, 2002). These drugs are often administered intrathecally. The intensity of chemotherapy in the consolidation phase may vary depending on patient risk (e.g. amount of leukemic cells are left in system; Westlake & Bertolone, 2002).

The final phase of chemotherapy is maintenance, and its purpose is to destroy the remaining cancer cells (American Cancer Society, 2009). It is designed to provide a prolonged period of therapy to destroy all remaining cancer cells, and is associated with daily therapy. The maintenance phase often includes daily oral doses of chemotherapy (e.g. mercatopurine) in combination with methotrexate (Westlake & Bertolone, 2002). Other drugs may be administered as well during maintenance if the patient has a higher risk or an increased chance of relapse.

It is important to note that while chemotherapy is a very effective treatment for ALL, it is associated with dangerous and uncomfortable side effects. Common immediate side effects of chemotherapy include hair loss, mouth sores, loss of appetite, diarrhea, nausea, lowered resistance to infection, bruising, easily bleeding, and fatigue (American Cancer Society, 2009). The drugs used in chemotherapy are toxic to cancer cells, which makes them effective at eradicating the disease, but the drugs are also toxic to normal cells, subsequently harming the patient while curing him or her (Rodman & Reed, 2000). In modern medical research, certain drugs have been discovered that are very effective at killing cancer cells, but are also highly toxic to healthy cells. A good example of this is methotrexates. Methotrexates are a type of chemotherapy agent used to treat many cancers, including ALL, in the pediatric population. It destroys cancer cells by interfering with folic acid (Rodman & Reed, 2000). This quality has been associated with very effective treatment of ALL, as methotrexates have proved to be highly toxic to leukemic cells (Cheok & Evans, 2009). However, methotrextates have also proved to be highly toxic to normal cells, resulting in both short term and long term serious side effects

(Rodman & Reed, 2000). Immediate complications include nausea, vomiting, low blood counts, mouth sores, and skin rashes. These side effects are common in many chemotherapy agents. However, long term side effects have been discovered as well, including seizures, intellectual impairment, kidney damage, and liver damage. Since the side effects are so serious, the use of methotrexates is monitored carefully; however, it is so effective that it is commonly used in chemotherapy.

Thus, balance is crucial in the administration of chemotherapy; treatment protocols are balanced to use the least amount of chemotherapy possible in order to treat an individual‟s ALL in order to reduce toxicity to normal cells (Cheok & Evans, 2009).

Radiation.

Radiation therapy is the use of high-energy radiation to kill cancer cells (American Cancer Society, 2009). Children diagnosed with ALL who receive radiation therapy typically have cancer that has spread to the membranes which cover the brain or testicles. It may also be used in children who were originally treated with ALL but who experienced a relapse of the disease affecting the CNS or testicles (Cullen et al., 2002).

In the past, radiation therapy was one of the most preferred methods of treatment for children diagnosed with ALL. Like other treatments which kill both cancerous and non-cancerous tissue, non-cancerous tissue destroyed by radiation recovers much better than cancerous tissue (Merchant, 2000). This makes radiation an effective treatment for many cancers, ALL included. Radiation to the brain also proved to decrease the risk of cancer relapse (Merchant, 2000).

However, current research has shown that radiation may cause problems in learning and growth (American Cancer Society, 2009; Merchant, 2000). Even at very low doses, radiation has been shown to be responsible for long-lasting cognitive and physical side effects (American Cancer Society, 2009). Additionally, an increase in dosage is correlated with more significant impairments (Weiner & Simone, 2003). Thus, treatment teams working with children diagnosed with ALL typically tend to discourage the use of radiation unless other treatments with less severe side effects (e.g. chemotherapy) are not effective in treating the disease (Merchant, 2000).

Transplants.

A small percentage of children diagnosed with ALL require more extreme treatment than chemotherapy or radiation can provide. Children whose chances of survival are slim with chemotherapy, radiation therapy, or a combination of the two, are eligible for bone marrow or stem cell transplants. Children whose ALL recurs within 6 months or less following remission are also often treated with transplants (American Cancer Society, 2009; Horwitz, 2000). The goal of both bone marrow and stem cell transplants is to use extreme chemotherapy to destroy all of the cancer and then provide the child with healthy blood-forming cells to recover from the damage caused by the cancer-killing drugs.

Prior to the transplant, children are given extremely high doses of chemotherapy which destroys all of the cancerous cells. However, the doses are so high that the chemotherapy also destroys many of the cells in the bone marrow which is why these

individuals necessitate a bone marrow or stem cell transplant (American Cancer Society, 2009). Bone marrow transplants use healthy bone marrow cells from a donor (allogeneic transplant), from the patient (autologous transplant) or from an identical twin (syngenic transplant; Horwitz, 2000). Stem cell transplants use blood-forming stem cells with the hope that within 3 to 4 weeks the stem cells will begin to produce healthy blood cells in the child‟s bone marrow (American Cancer Society, 2009). As with bone marrow transplants, stem cell transplants may be allogeneic or autologous, however, the autologous stem cell transplants are less commonly used because a child‟s own stem cells may contain cancer (American Cancer Society, 2009).

Current Treatment Protocols.

Over the last several decades, the treatment of ALL has taken great strides. The general rule that treatment teams abide by when making decisions about an individual‟s treatment is to provide the least aggressive approach possible to reduce neurotoxicity (Pui, 2000). In over 80% of cases, chemotherapy alone is successful in eradicating the disease (Pui, 2000).

When a child is referred to an oncologist and a diagnosis of ALL is confirmed, the typical first step in treatment is to clear the child of any current infection (e.g., fever) before beginning chemotherapy. Once this is complete, the induction phase of chemotherapy can begin in which the child typically is given a corticoid (e.g. prednisone) with vincristine and L-asparaginase, sometimes accompanied with anthracycline. With this treatment protocol, 97 to 99% of patients will attain complete remission (Pui, 2000).

The induction phase usually lasts around 6 weeks for patients with ALL (Cheok & Evans, 2009). Then, the consolidation phase of chemotherapy is administered, which continues to reduce cancerous cells. The typical drugs used in this phase are methotrexates and mercpatopurene, and this phase typically lasts roughly 2 weeks (Cheok & Evans, 2009; Pui, 2000). Then, the continuation treatment, or maintenance phase is administered. The continuation phase typically involves daily administration of mercaptopurine combined with weekly administration of methotrexates (Cheok & Evans, 2009; Pui, 2000).While many pediatric cancers utilize induction, consolidation, and continuation phases of chemotherapy to eradicate the disease, ALL requires a much longer continuation phase than other types of pediatric cancers.

ALL has been treated with chemotherapy only in the last 50 to 60 years (Rodman & Reed, 2000), and it has become the preferred method of treatment for these patients. The use of current treatment protocols involving combination chemotherapy, as described above has been continually improved to arrive at the current survival rates of 80%. Typically, doctors will use combination chemotherapy alone to treat ALL in an individual if possible, using other methods of treatment (radiation, transplants) only when necessary (Cheok & Evans, 2009). Some of the most recent ALL treatments are being informed by genetic markers which indicate certain factors, influencing which agents to use. For instance, certain genetic markers in an individual may indicate increased resistance to a certain drug or exaggerated toxicity with another drug. Thus, the genetic markers can assist treatment teams in providing the safest, most effective treatment to

individuals (Cheok & Evans, 2009). In the future, particular treatment protocols may be designed and implemented based on genetic screening upon diagnosis.

Late Effects of Treatment for ALL

While the treatment for ALL (e.g., chemotherapy, radiation) is effective at killing cancerous cells, it is also effective at damaging normal tissue. Late effects of treatment are negative effects caused by the injury that the cancer treatment causes to the healthy cells in the body (American Cancer Society, 2009). Factors that contribute to late effects include lack of cell nourishment, chronic cell injury, death of healthy cells, and scar tissue. Chemotherapy damages healthy cells by killing healthy cells along with cancerous cells. Radiation damages healthy cells by using high energy rays to kill cancer cells, which damages normal cells as well. While general consensus states that late effects are more severe in patients treated with radiation and chemotherapy when compared to patients treated with chemotherapy only, recent literature indicates that neuropsychological deficits do occur in patients treated only with chemotherapy (Hobbie, Ruccione, Harvey, & Moore, 2002).

While there are immediate effects of treatment (e.g. nausea, fatigue, pain, etc.), late effects typically do not show up immediately following completion of treatment (Weiner & Simone, 2003). These effects are called *late effects* because they typically appear within 2 to 5 years following completion of treatment (American Cancer Society, 2009).

Late effects can be seen in physical, cognitive, and psychological realms. Physical late effects include injury to eyesight, hearing, growth, thyroid, sexual development, cardiovascular system, respiratory system, muscles, bones, and teeth (American Cancer Society, 2009). Neuroanatomic late effects can be present as well after treatment for ALL, and may include diffuse brain atrophy, perfusion defects, and decreased white matter (Hobbie et al., 2002). In children treated for ALL, it is hypothesized that methotrexates (used in chemotherapy) are responsible for perfusion defects (Hobbie et al., 2002). Perfusion refers to blood flow in the brain; too little perfusion pressure restricts blood to the brain and too much perfusion pressure can increase intercranial pressure. The most common cognitive late effects following treatment for ALL are deficits in attention and memory; other cognitive late effects can include a decline in academic achievement, fine motor functioning, processing speed, and visual-perceptual skills. Children treated for leukemia, including ALL, are susceptible to cognitive late effects of treatment (Weiner & Simone, 2003). When including all children created for cancer, roughly 50 to 60% will have risk of neurocognitive impairment following treatment (Weiner & Simone, 2003).These neurocognitive late effects, along with other cognitive late effects, will be discussed in detail. Emotional late effects such as anxiety or depression may be present as well. Late effects are most commonly seen in individuals who receive treatment directly to the central nervous system (e.g. intrathecal chemotherapy, radiation to brain; American Cancer Society, 2009). Pediatric patients with ALL are more susceptible to late effects of treatment because children and adolescents have not completed growth and development (Cullen et al., 2002).

Demographic Considerations.

ALL can affect children and adolescents of both genders, any age, and any ethnicity. However, rate of diagnosis, susceptibility to late effects, survival rates, and reaction to treatment can vary greatly across demographic differences.

Age at Diagnosis.

While there are some discrepancies between studies, it is generally reported that ALL is most frequently diagnosed between ages 2 and 5 years (Pui, 2000; Raccione, 2002; Westlake & Bertolone, 2002). While ALL can affect individuals of all ages, it typically affects young children the most. Survival rates of ALL are the highest in children in the youngest age group (ages 1-4 at diagnosis; survival = 85%), and survival rate steadily declines as the age at diagnosis increases (Westlake & Bertolone, 2002). It is hypothesized that the different age groups (1-4 years, 5-9 years, 10-14 years, and 15-19 years) may be typified by different biologic subtypes that are associated with different survival rates (Westlake & Bertolone, 2002).

While young children with ALL have the highest survival rates, they also have the highest levels of susceptibility for developing late effects. Late effects are most common in children who are 5 years or younger at the time of treatment (American Cancer Society, 2009). Cognitive late effects are particularly salient for the younger age group (Brown et al., 1998; Hobbie, 2002; Von der Weid et al., 2002; Weiner & Simone, 2003). While late effects can also be present in survivors of ALL in the older age at diagnosis groups, the younger ages at diagnosis correlate to more severe cognitive late effects

(Eiser, 1998). Even very low doses of treatment have been shown to cause late effects in very young children (Waber, 200).

A study by Leung, Hudson, Zhu, Rivera, Riveiro, Sandlund et al (2000) investigated academic late effects in survivors of ALL who received radiation treatment at ages 2 years and younger. They discovered that for this particular set of patients, there was an 18% increase in academic difficulties for each month younger in age when radiation was received. For example, a child who received radiation at 15 months will have an 18% decrease in academic functioning when compared to a child who received radiation at 16 months.

It is hypothesized that younger children are more vulnerable to late effects due to rapid growth and development that occurs at younger ages (Leung et al., 2000). Young children are often treated during critical developmental periods, which may be interrupted (Weiner & Simone, 2003) by the acquired insult of cancer treatment. When a young child is diagnosed with ALL, both the disease and the treatment potentially interrupt typical growth and development.

Gender.

Cancer incidence is generally higher for males than females, and this is true for ALL as well (Raccione, 2002; Westlake & Bertolone, 2002). In children diagnosed with ALL, there are slightly higher survival rates for females than males (Westlake & Bertolone, 2002). However, female survivors of ALL are more susceptible to developing more severe late effects than their male counterparts (Butler, Rizzi, & Bandilla, 1999;

Gamis & Nesbit, 1991; Leung et al., 2001; Palmer et al., 2001; Ris, Packer, Goldwien, Jone-Wallace, & Boyett, 2001; Spencer, 2006). A meta-analysis by Peterson et al. (2008) confirmed the increased severity of late effects in female survivors when compared to male survivors. The greater risk of late effects for females appears to be present among survivors who received radiation and chemotherapy, and survivors who received chemotherapy alone (Von der Wied et al., 2002). Hobbie, Ruccinone, Harvey & Moore (2002) report that females have a greater risk of developing general cognitive deficits, but do not show difficulties in language based academic skills (e.g. reading). Brown et al. (1998) report that females displayed significant difficulties on test of nonverbal skills when compared to age-matched norms, whereas males did not show significant difficulties.

Ethnicity.

While ALL affects children in all countries, differences have been found among ethnic origins. Raccione (2002) reported that children of African descent have lower incidence of diagnosis of ALL than children of Caucasian descent. Westlake & Bertolone (2002) concur, stating that ALL is most common in Caucasian children.

Cognitive Late Effects.

Over the past several decades, while treatment for ALL has improved survival rates dramatically, cognitive late effects have been discovered. Many researchers have documented long-term cognitive effects on attention, memory, nonverbal functioning, fine motor functioning, academic achievement, and overall cognitive functioning (e.g.,

Askins & Moore, 2008; Cullen et al., 2002; Leigh, 2000). While these late effects appear to be more severe following radiation treatment, many cognitive late effects have also been found to be present following chemotherapy alone, particularly when methotrexate is part of the treatment regimen.

IQ.

While most researchers agree that chemotherapy alone is less damaging to cognitive abilities than radiation plus chemotherapy, some evidence for overall cognitive decline following chemotherapy regimens does exist. Meta-analysis indicates that, when compared to healthy controls, survivors of ALL treated only with chemotherapy demonstrate significantly lower IQs, as measured by the Wechsler tests (Peterson et al., 2008).

Attention.

Attention is the ability to focus concentration on one portion of the environment at the exclusion of others. Attention is an important ability which impacts both daily and academic functioning. Among survivors of ALL, a deficit in attention following completion of treatment is one of the most common late effects.

Survivors who underwent protocols including radiation therapy as well as protocols including only chemotherapy show deficits in overall cognitive ability and attention (Cullen et al., 2002). While it has been concluded that late effects are more severe among survivors who receive radiation as compared to survivors who receive

chemotherapy alone, it has been shown that attention is still negatively affected in the chemotherapy only group (Ashford et al., 2010; Kingma et al., 2002; Moleski, 2000; Reddick et al., 2006; Spencer, 2006; Waber, 2002). These attention deficits have been shown to significantly impair academic and home functioning. Weiner & Simone (2003) found that many nonverbal functions, especially attention, are impacted by the treatment of ALL.

Specific deficits in attention are rarely found shortly following completion of treatment. It is common to see deficits in attention beginning 3 to 5 years after treatment for ALL has been finished (Hobbie et al., 2002). Jain, Brouwers, Okcu, Cirino, and Krull (2009) found differential attentional deficits in males and females with significantly worse performance in both sexes to be correlated with intensity of treatment. Specifically, they found that females performed worse on measures related to the anterior attention system (shifting attention) and subcortical attention (sustaining attention) whereas males performed worse on measures related to anterior control (inhibition and working memory).

Memory.

Memory is a broad ability describing an individual‟s ability to retain knowledge and information. There are many different types of memory (e.g. short-term, long-term, episodic, semantic, explicit, implicit), and memory is a complex neurological entity. Memory involves several areas of the brain, including the hippocampus, frontal lobes,

and the thalamus (Carlson, 2007). Memory also involves several complex processes, including consolidation and retrieval, in order to work properly.

As with attention, memory is negatively affected by treatment for ALL (Askins & Moore, 2008). Individuals who undergo radiation as well as individuals who undergo chemotherapy alone have significant declines in memory functioning post-treatment (Waber, 2002). Research has shown that both verbal memory (Waber, 2002) and spatial memory (Spencer, 2006; Weiner & Simone, 2003) are diminished in survivors of ALL. Memory deficits are considered late effects in survivors of ALL because they typically surface 3 to 5 years following the completion of CNS treatment (Hobbie et al., 2002).

Processing Speed.

Reduction of white matter in the brain (which will be discussed below) leads to less efficient processing of information. White matter volume is typically reduced by treatment for ALL, leading to late effects in the area of processing speed, as the brain is less efficient following treatment. Processing speed deficits have been found in children treated with only chemotherapy (e.g. Ciesielski et al., 1999; Heukrodt, Powazek, Warren, & Kennely, 1988). Additionally, a study by Mennes et al. (2005) indicated that processing speed abilities in survivors of ALL were significantly impaired and decreased as task difficulty increased.

Nonverbal Functioning.

Nonverbal skills include short-term visual memory, processing speed, visual-motor integration, sequencing ability, attention, and concentration (Weiner & Simone, 2003). Nonverbal skills typically measured by cognitive testing include copying or making designs and solving visual puzzles.

As with other typical late effects, nonverbal late effects generally appear 3-5 years following completion of CNS treatment in survivors of ALL. Among common late effects, it appears that nonverbal late effects are more common across ALL survivors than verbal late effects (Weiner & Simone, 2003). Nonverbal late effects are present in survivors who received only chemotherapy (no radiation; Brown et al., 1992). A study conducted by Brown et al. (1998) suggests that there is an interaction between gender and nonverbal late effects, with females performing significantly worse than males on measures of nonverbal performance. This is consistent with overall findings that females may be more susceptible to cognitive late effects than males.

Fine Motor Functioning.

Fine motor functioning, usually measured by motor speed, gnosis, and strength is found to be impaired in survivors of ALL and, like processing speed, may be contributable to reduction of white matter in the brain (Aukema et al., 2009). Fine motor skills are important in academic skills such as writing and typing. They are also important in home living skills such as dialing a telephone, getting dressed, and performing hygiene skills.

Fine motor skill defects typically begin to show 3-5 years following completion of treatment. Deficits are present in survivors who received only chemotherapy (no radiation; Jansen et al., 2008; Kaleita, Reaman, & MacLean, 1999; Moleski, 2000;).

Academic Achievement.

Survivors of ALL typically display below average academic performance when compared to their peers. Late effects appear to be present across academic subjects. Survivors of ALL were found to have significantly lower academic performance as soon as 4 years post-diagnosis (Brown, Sayer, Antoniou, Toogood, & Rice, 1999). Brown et al. (1999) found deficits in math, reading, and spelling and Peterson et al. (2008) reported math and reading problems in survivors of ALL. However, many researchers are discovering that mathematics is more affected than other areas of academic achievement in survivors of ALL. Mathematics learning disabilities were found in survivors of ALL who were treated with chemotherapy only, as reported by Brown, Madan-Swain, Pais, Lambert, Sexson & Ragab (1992). Additionally, a comprehensive review of literature by Moleski (2000) confirmed that while academics in general are impacted by treatment for ALL, mathematics continually appears as a specific deficit.

Academic deficits may be caused by a number of reasons. Since late effects are present in a number of higher order skills (e.g. attention, memory, executive function), it may be hypothesized that the late effects in other cognitive skills has a negative impact on academic skills. For example, if a child has difficulty with short term memory and attention, a skill such as performing mental calculations may be very difficult. Mental

calculations require the child to attend to and remember the problem, in addition to carrying out the academic skill (algorithm) to solve the problem. Spencer (2006) also found that mathematics achievement was especially impacted by CNS treatment (e.g. chemotherapy).

Neurophysiological Abnormalities.

Neurophysiological abnormalities have been shown to occur in survivors of ALL. Ueberall et al. (1997) report that 53% of survivors of ALL have abnormal results on neurophysiological measures. Among survivors, individuals treated with both radiation and chemotherapy show the most neurophysiological abnormalities, followed by individuals treated with radiation only, followed by individuals treated with chemotherapy only (Hertzberg et al., 1997).

Treatment for ALL, including chemotherapy, radiation therapy, and supplemental steroids may be associated with reduced cortical white matter volume, particularly in the right prefrontal cortex (Carey et al., 2008; Reddick et al., 2006). It is believed that reductions in white matter volumes as a result of treatment neurotoxicity contribute to observed declines in various domains of neurocognitive functioning, including speed of information processing and executive functions (e.g. planning, attention) (Carey et al., 2008; Mulhern & Palmer, 2003). Reduced white matter volume is most severe in individuals who were treated with radiation in addition to chemotherapy (Porto et al., 2008), however, significant white matter reduction is present in those treated only with chemotherapy (Aukema et al., 2009; Ficek et al., 2010). Additionally, many studies

investigated and directly correlated white matter reduction to reduce cognitive abilities in the areas of overall cognitive performance (Kesler, Tanaka, & Koovakattu, 2010), processing speed (Aukema et al., 2009), attention (Reddick et al., 2006), and working memory (Ashford et al., 2010).

While white matter represents the most affected area of morphological changes in the brain of ALL survivors, some research indicates morphological changes in the frontal lobes and cerebellum. Some researchers theorize that acquired injuries in early childhood, like treatment for ALL, disrupt the developmental trajectory of neural growth and affect the frontal lobes and cerebellum in particular (Ciesielski, Harris, Hart, & Pabst, 1997; Horska et al., 2010; Lesnik, Ciesielski, Hart, Bensel, & Sanders, 1998). Results indicated that the most damage to these areas of the brain occurs when the insult occurs before age 5, which is precisely when many individuals with ALL are diagnosed and begin treatment.

Other neurophysiological (non-morphological) changes in the brain have been found, which may be precursors to cognitive late effects. There is evidence for impaired cerebral blood flow that occurs during treatment (Osterlundh et al., 1999). Additionally, biochemical changes that are precursors to brain damage have been found in the cerebro-spinal fluid during induction chemotherapy (Osterlundh et al., 2008). These changes during chemotherapy may be precursors to changes in white matter and other brain areas later on, however, the exact mechanisms are not yet known.

Working Memory

Working memory is the ability to temporarily store and cognitively manipulate information after a single presentation (Floyd, 2003). Verbal working memory (Baddeley, 1992) is activated when the presentation of information is heard, and visual working memory is activated when the presentation of information is seen. Working memory differs from other types of memory in that: 1) it manipulates incoming information and 2) the information dissipates within several seconds unless rehearsed (Towse, Hitch, & Hutton, 2000).

The most common theory of working memory was introduced by Baddely and Hitch in 1974. They outlined three components of working memory: the phonological loop, the visuospatial sketchpad, and the central executive. Recent revisions to this theory add a fourth component, the episodic buffer (e.g., Baddeley & Larsen, 2007). Working memory additionally accesses prior knowledge and long-term memory. This theory of working memory, as well as the existence of its components is well-supported by research (e.g., Baddeley et al., 1984; Baddeley & Hitch, 1994; Bishop & Robson, 1989).

The three main components of working memory work together to store and manipulate information. The central executive system supervises and controls the information that goes to and from the other components (phonological loop, visuospatial sketchpad, and episodic buffer). The phonological loop of working memory is activated by verbal and acoustic information. Once the information is heard, it enters a system that temporarily stores and rehearses it (Baddeley, 2000). Essentially, the phonological loop

holds the information once it is presented verbally. The visuospatial holds visually presented information (Baddeley, 2000). The newest proposed component of working memory, the episodic buffer, integrates incoming information (auditory and visual) with long term memory and semantic meaning (Baddeley, 2000).

Recent revisions to this theory add a fourth component, the episodic buffer (Baddeley & Larsen, 2007). This revision proposes that working memory additionally accesses prior knowledge and long-term memory. The episodic buffer integrates incoming information (auditory and visual) with long term memory and semantic meaning (Baddeley, 2000).

A common measure of working memory is verbal presentation of a string of numbers that an individual needs to present in reverse order (Ackerman, Beier, & Boyle, 2005). This particular task is present on many instruments that measure working memory in children (e.g., Woodcock-Johnson III, Weschler Intelligence Scale for Children, Fourth Edition, Differential Ability Scales, Second Edition, Test of Memory and Learning, Second Edition). For instance, on the Woodcock-Johnson III Tests of Cognitive Abilities (WJ-III Cog), the working memory cluster is comprised of 2 subtests: numbers reversed and auditory working memory. Numbers reversed is the task mentioned above, and auditory working memory is a task in which the subject hears works and numbers and repeats the words, then numbers in the order presented (Schrank, Flanagan, Woodcock, & Mascolo, 2002). Both tasks require that the subject manipulate orally presented information. There are also subtests in some batteries (e.g. TOMAL-2)

that measure visual working memory. These subtests generally require the subject to watch the examiner manipulate objects in a particular sequence, and then the subject either repeats the sequence or performs it in the reverse order as was presented. A different way to measure visual working memory is to require the subject to look at a series of images, then manipulate them mentally (e.g. put in a different order, reverse the order).

Deficits in working memory can manifest in various parts of academic and every-day life. Academically, working memory deficits seem to appear most clearly in mathematics performance, and most research linking working memory deficits to academic difficulties focus specifically on mathematics.

Many studies have shown that children who have specific math learning disorders (MLD) have concurrent deficits in working memory abilities. Strengths in mathematics ability has also been positively linked to working memory ability (Dark & Benbow, 1991). Geary et al. (1999) found that errors in mathematical problems (e.g. arithmetic, simple operations) that children with MLD make are due to insufficient working memory and executive functioning. Geary et al. (1999) concluded that executive functioning, especially working memory, contribute to mathematical deficits in children with MLD.

Other studies have linked working memory to all children on certain mathematical tasks, such as story problems and mental addition (Adams & Hitch, 1997; Gruber, Indefrey, Steinmetz, & Kleinschmidt, 2001). Math word problems (also referred

to as story problems) are of particular interest to many researchers because of the seemingly complex nature of their presentation (whether oral or visual). In order to solve a math word problem, and individual not only has to read (or hear) and understand the problem, but convert the problem to mathematical terms, from which the problem can be solved. Executive processes, such as selective attention, are likely used to solve math word problems, which implicates the role of working memory as an important component in this process (Hale et al., 2003). Neuroimaging studies show that solving math word problems activates the frontal lobe, in particular Broca‟s area (Gruber, Indefrey, Steinmetz, & Kleinschmidt, 2001); the frontal lobe is responsible for executive processes and working memory, and Broca‟s area in particular is responsible for interpreting auditory information.

While difficulties in mathematics are the most commonly seen and studied, other areas of academic achievement may be affected by working memory deficits as well. Difficulties with reading comprehension are connected to working memory difficulties (Caretti, Borella, Cornoldi, & De Beni, 2009). Both specific parts of working memory (e.g. attentional levels, auditory vs. visual working memory) and working memory levels in general are accurate predictors of difficulty with reading comprehension.

A study conducted by Alloway (2009) determined that working memory levels predicted individuals with learning difficulties better than overall IQ. This indicates that working memory deficits are significantly related to learning problems, such that children

with diminished working memory are significantly more likely to have academic difficulties.

Gathercole (2008) described working memory deficits in the classroom, and determined that children with poor working memory skills show difficulty learning across academic subjects (reading, math, science, social studies, etc.) and that these deficits impact children in both primary and secondary grades. Gathercole describes academic difficulties due to working memory deficits as an overload on the working memory system, in which information is received by an individual with working memory deficits, but it is lost before it can be manipulated, leading to impaired achievement.

Working memory is a complex, important cognitive skill, and is involved in other cognitive and neurological processes, including auditory processing and attention.

Statement of the Problem

Recent improvements in the treatment of ALL have led to greatly increased survival rates; approximately 85% of children diagnosed with ALL will survive 5 years or more. Along with a greater number of survivors of ALL has come a greater incidence of late effects. Cognitive late effects, particularly with memory and attention, have been recently documented in survivors of ALL. However, since the greater incidence of survivors and discovery of cognitive late effects is a relatively recent phenomenon, all late effects in survivors of ALL have not been documented. Late effects in attention and memory have been well documented, but working memory, which is primarily comprised of attention and memory, has not been documented in relation to late effects. This study

aimed to help fill this gap in the research. Specifically, this study investigated potential late effects on the specific cognitive ability of working memory.

Research Questions and Hypotheses

Research Question 1

Is working memory negatively impacted by the treatment of ALL in survivors of pediatric ALL?

Hypothesis 1a.

It is expected that, when compared to their overall cognitive functioning as measured by psychometric intelligence, survivors of ALL will demonstrate significantly impaired working memory functioning.

Rationale 1a.

Research has shown that the treatment of ALL potentially leads to cognitive late effects due to the toxicity of treatment (Hobbie et al., 2002; Weiner & Simone, 2003). Two of the most common late effects are deficits in memory and attention among individuals who received treatment for ALL (Askins & Moore, 2008; Cullen et al., 2002). Additionally, overall cognitive functioning is less impaired than specific abilities in individuals who received treatment. Given that both memory and attention are major components of working memory (Baddeley, 1992), it is expected that working memory will also be negatively affected when compared to overall cognitive functioning.

Hypothesis 1b.

It is expected that, when compared to a normative sample, survivors of ALL will demonstrate significantly impaired working memory functioning.

Rationale 1b.

Research has shown that both memory and attention are impaired in individuals who received treatment for ALL (Askins & Moore, 2008; Cullen et al., 2002). Given that both memory and attention are major components of working memory (Baddeley, 1992), it is expected that working memory will also be negatively affected when compared to normative controls.

Research Question 2

Is there a difference in working memory functioning between male and female survivors of ALL?

Hypothesis 2.

It is expected that females will perform significantly worse on measures of working memory than males.

Rationale 2.

Research has shown that females consistently display more severe cognitive late effects than males (Butler et al., 1999; Gamis & Nesbit, 1991; Leung et al., 2001; Palmer et al., 2001; Ris et al., 2001; Spencer, 2006). Although males have higher rates of

diagnosis and morbidity, females have more severe cognitive late effects, even when treatment is less intense (Raccione, 2002; Westlake & Bertolone, 2002).

Research Question 3

In survivors of ALL, is there a difference between verbal and nonverbal working memory performance?

Hypothesis 3.

It is expected that, in survivors of ALL, nonverbal working memory performance will be significantly worse than verbal working memory performance.

Rationale 3.

Among late effects, general consensus dictates that nonverbal (e.g. spatial) performance is more severely impacted than verbal performance (Brown et al., 1998; Hobbie et al., 2002; Weiner & Simone, 2003). Nonverbal abilities include processing speed, short term memory, visual motor integration, and sequencing ability (Hobbie et al., 2002).

Chapter III: Method

Participants

Participants were 19 individuals ages 6 to 21 years who were designated as survivors of pediatric Acute Lymphoblastic Leukemia (ALL) by the LIVESTRONG Survivorship Center at Dell Children‟s Medical Center in Austin, Texas (hereafter referred to as LIVESTRONG). Patients were typically designated as survivors once they have completed treatment and are cancer-free for roughly one year. The following inclusion criteria applied: Participants must be (a) post-treatment and in survivorship for pediatric ALL, (b) between 6 and 21 years of age, and (c) English-speaking. Individuals meeting school criteria as having a visual or auditory impairment were not included as participants in this study. Additionally, individuals who were undergoing treatment for ALL at the time of the study, who underwent a bone-marrow transplant, had a recurrence of cancer, or who had impaired global cognitive functioning (e.g. mental retardation) were not included in this investigation.

Instrumentation

Wechsler Abbreviated Scale of Intelligence.

The Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) is a brief, reliable measure of intelligence that can be used with individuals ages 6-89 years. It is comprised of four subtests that are parallel to subtests found on the more detailed Wechsler intelligence tests (Wechsler Intelligence Scale for Children, 4th Edition;

Wechsler Adult Intelligence Scale, 4rd Edition). Intended use of the WASI includes brief assessment of an individual‟s overall level of cognitive functioning. Administration requires approximately 30 to 45 minutes. The WASI contains four subtests; two of the subtests measure verbal performance (Vocabulary, Similarities) and two of the subtests measure nonverbal performance (Block Design, Matrix Reasoning). Vocabulary requires the child to define orally and graphically presented words. The Similarities subtest requires the child to answer questions about how two objects or concepts are alike. Block Design requires the child to reproduce designs quickly using blocks. Matrix Reasoning requires the child to determine a piece of a missing visual matrix from an array of answer choices (Sattler & Dumont, 2004). All four subtests were administered in this study to obtain an estimate of verbal functioning (VIQ), nonverbal/visual-spatial functioning (PIQ) and overall psychometric intelligence (FSIQ). The WASI was normed according to the 1997 census data. The normative sample included 2, 245 children and adults which was stratified based on geographic region, age, sex, ethnicity, and education level. The WASI demonstrates adequate reliability across both children (ages 6-16) and adults (ages 17-89). For children, the reliability for the IQ score ranges from .92 to .95, and for adults ranges from .96 to .98.

Wechsler Intelligence Scale for Children - Fourth Edition.

The Wechsler Intelligence Scale for Children - Fourth Edition (WISC-IV; Wechsler, 2003) is an individually administered instrument used to assess psychometric intelligence with children ages 6 to 16 years. The WISC-IV was normed using national

standardization samples which represent the United States population based on the March 2000 census. The normative sample was stratified based on age, sex, race, parent education level, and geographic region (Wechsler, 2003). Although the WISC-IV contains 15 subtests, only one subtest was used in this study. The Digit Span subtest, which is used to measure an individual"s working memory, was administered. This subtest required the child to listen to and repeat strings of numbers, both in forward and reverse order (Sattler & Dumont, 2004). This subtest has two portions: digit span forward and digit span backward. A process score was derived for each child"s digit span backward (DSB) because this portion of the subtest is a better estimate of working memory than digit span forward. The process score was derived using the raw score of the DSB portion of the subtest and was translated using table A.8 in the WISC-IV scoring manual (Wechsler, 2003). The Digit Span subtest is a reliable measure, having the following reliabilities: Internal Consistency: .87; Test-Retest Reliability: .81. The process scores display strong reliability was well, ranging from .72 to .82 across ages 6 to 16.

Test of Memory and Learning, Second Edition.

The Test of Memory and Learning, Second Edition (TOMAL-2; Reynolds & Voress, 2007) is a standardized battery used to measure different memory functions in individuals ages 5 to 59 years. The TOMAL-2 was normed using a standardization sample of 1,961 individuals residing in 28 states. The sample was stratified based on the 2002 census and the following demographic characteristics were considered: gender, race, socioeconomic status, parent level of education, geographic region, exceptionality

status, and age (Reynolds & Voress, 2007). The TOMAL-2 includes 8 core subtests and 6 supplementary subtests; however, this study only used 2 subtests: Visual Sequential Memory and Letters Backward. These subtests provided estimates of verbal and nonverbal working memory. Visual Sequential Memory required the examinee to recall a sequence of designs in a particular order. Letters Backward required the examinee to recall a string of letters in reverse order. Adequate reliability is present for both subtests. Visual Sequential Memory reliability estimates range from .78 to .92 for ages 6-18. Letters Backward reliability estimates range from .87 to .98 for ages 6-18.

Procedure

Approval by Human Subjects Committee.

This study complied with ethical standards posed by the American Psychological Association, the University of Texas at Austin, and Seton Family of Hospitals. On December 17, 2009, the Departmental Review Committee of the Department of Educational Psychology and the Institutional Review Board approved the study. Parents/guardians of each child participant signed an IRB-approved consent form and each child participant signed a form of assent. The consent form can be found in Appendix A and the assent form can be found in Appendix B.

Recruitment of Participants.

Participants were recruited through the LIVESTRONG center in Austin, Texas. Children who were designated by their oncologists as survivors of pediatric ALL and

who met the inclusion criteria were invited to participate in the study. Participants were identified and attained through LIVESTRONG in one of two ways. Participants were either (1) individuals who were newly identified by a LIVESTRONG oncologist as meeting survivorship criteria (hereafter referred to as a New Survivor) or (2) individuals who were previously identified by a LIVESTRONG oncologist as meeting survivorship criteria and were scheduled for an annual follow-up meeting (hereafter referred to as Follow-Up Survivor). New Survivors were referred for neuropsychological evaluation by their LIVESTRONG pediatric oncologist as a component of their direct survivorship services, whereas Follow-Up Survivors were recruited prior to their annual LIVESTRONG checkup and neuropsychological reevaluation. New and Follow-Up Survivors were invited to participate in the current study in which they received a full neuropsychological evaluation, integrated report, and feedback at no charge in exchange for their consent and assent.

Once identified as meeting criteria for the study, the guardians of potential participants (or participants if age 18 or older) were provided with a flyer that gave a brief description of the study, primary investigator contact information, and space for the individual to provide contact information. The potential participants, or their guardian, were asked to return the flyer using a pre-paid envelope or in person. In total, 65 individuals were identified through LIVESTRONG that met study criteria and were subsequently given study flyers. Of these 65 individuals, 25 returned flyers to the primary investigators. Three individuals declined to participate or were non-responsive to the investigators contact, one child was excluded due to a diagnosis of mental retardation,

and one child died before she could participate in the study. One child was excluded due to radiation during treatment for cancer; this information was discovered following the neuropsychological evaluation and his data was forthwith removed. Therefore, the total number of participants in the study amounted to 19 individuals.

Data Collection.

Children whose parents gave consent to participate and met inclusion criteria and young adults (ages 18-21) who gave consent and met inclusion criteria were participants of this study. Once consent was given, the parent or guardian of the child scheduled an appointment with the principal investigator for the child to participate in a full neuropsychological evaluation. The evaluation took place in a quiet, private room in the Children‟s Blood and Cancer Center in the Specially for Children building at Dell Children‟s Hospital in Austin, Texas. The child engaged in a one-on-one neuropsychological evaluation with the principal investigator for approximately 120-150 minutes while the parent/guardian waited in a waiting area and filled out parent forms. The child was allowed take breaks as needed during testing.

The neuropsychological evaluation provided estimates of each participant‟s psychometric intelligence, verbal performance, nonverbal performance, academic achievement, short-term memory, delayed memory, working memory, processing speed, executive function, and emotional functioning. Although this study only used data from three instruments, other measures were used for the purpose of the evaluation. These instruments are: Wide Range Achievement Test, Fourth Edition (WRAT-4; selected

subtests), Test of Memory and Learning, Second Edition (TOMAL-2; selected subtests), Wechsler Intelligence Scale for Children – Fourth Edition (WISC-IV; selected subtests), Differential Ability Scales, Second Edition (DAS-II; selected subtests), Halstead-Reitan Battery (selected subtests), Controlled Oral Word Association Test (COWAT), Behavior Rating Inventory of Executive Function (BRIEF; parent and teacher forms), Trail Making Test, and Behavior Assessment Scale for Children, Second Edition (BASC-2;parent, self, and structured developmental history forms).

The parent gave teacher forms to the participant‟s teacher, who, when consent was given, filled out and mailed the form in a self addressed, stamped envelope, back to the investigator. Upon completion of each evaluation, the principal investigator scored each measure and wrote an integrated report which included summaries of the child‟s neuropsychological functioning, implications for school and home functioning, and recommendations. The principal investigator was supervised by a Ph.D. level licensed neuropsychologist. When each report was complete, the parent/guardian was given the option of receiving feedback over the phone summarizing the results of the evaluation. Then, the parent/guardian received a copy of the report which the parent used as he/she wished.

Calculation of Composites.

Composite scores were used in the analyses in this study and were computed by transforming measures from standard and scaled scores to *z*-scores and then averaging the components to create a composite. Specifically, the Working Memory Composite

(WMC) was determined by converting the individual‟s scores from Digit Span Backward (DSB), Letters Backward (LB), and Visual Sequential Memory (VSM) to z-scores. The three z-scores were then averaged, comprising the WMC. The Verbal Working Memory Composite (VWMC) was calculated in a similar manner by converting the individual‟s scores from Digit Span Backward (DSB) and Letters Backward to z-scores and averaging the two scores. The Nonverbal Working Memory Composite (NVWMC) was calculated by converting the individual‟s score on Visual Sequential Memory to z-scores. All z-scores were calculated using the formula $z = (\chi - \mu)/\sigma$.

Chapter IV: Results and Analyses

This investigation was conducted to further research regarding working memory abilities in survivors of pediatric acute lymphoblastic leukemia who were treated with chemotherapy alone. Working memory performance was compared to the sample‟s mean cognitive abilities as well as the population‟s average performance. Additional comparisons of working memory performance in males versus females and verbal versus nonverbal working memory were analyzed. Power analysis indicated low power to find statistically significant results, so qualitative and supplementary analyses were conducted in addition to quantitative analyses. All statistical analyses were performed using SPSS (version 17.0).

Preliminary Data Analyses

Descriptive Statistics.

Means, standard deviations, and ranges for Full Scale IQ (FSIQ) and all subtests are reported in Table 1. As shown in Table 1, the sample‟s mean FSIQ was slightly higher than the population‟s FSIQ of 100. The Digits Reversed Process Score mean for the sample was below the population‟s mean of 10 and both the Letters Backward and Visual Sequential Memory means are slightly larger than the population mean of 10. Other descriptive statistics can be found in appendices C through F and intercorrelations between variables can be found in Appendix G. The descriptive statistics were calculated to obtain an overview of the data, as many of the analyses are qualitative.

Table 1
Descriptive Statistics of Variables

Variable	Mean (n = 19)	SD	Range
FSIQa	104.42	16.69	72 – 129
Digit Span Backward[b]	8.74	2.45	5 – 13
Letters Backward[c]	10.32	3.71	4 – 20
Visual Sequential Memory[c]	10.47	2.29	7 - 15

[a]As measured by the WASI; Standard score.
[b]Process score as measured by the WISC-IV/WAIS-IV; Scaled score.
[c]As measured by the TOMAL-2; Scaled score.

Assumptions of *t*-tests.

The data were examined for violation of assumptions required for *t*-tests. In order to accurately analyze data using *t*-tests, all variables must conform to the normality assumption (Urdan, 2010) which assumes that the data for each variable are normally distributed. The Kolmogorov-Smirnov Test of Normality was completed using SPSS version 17.0 and the following variables had a non-normal distribution: Letters Backward (LB), Working Memory Composite (WMC), and Verbal Working Memory Composite (VWMC). Upon further inspection, LB had a non-normal distribution with a positive skew. Since LB is part of both the WMC and VWMC composites, and both of the remaining variables comprising the composite were normally distributed (Digit Span Backward and Visual Sequential Memory), LB was modified using a Log10 transformation (Field, 2009). The Log10 transformation successfully resolved the concerns of non-normality. Once LB was transformed and the WMC and VWMC were

recalculated using these new values, all variables met the normality assumption for *t*-tests.

Power Analysis

Power is the ability to correctly reject a false null hypothesis when using statistical analyses. It relies on the effect size, alpha level, and sample size (Keith, 2006). Power analysis was conducted using GPower (version 3.0; Faul, Erdfelder, Lang, & Buchner, 2007) in order to determine the necessary sample size to detect significance using *t*-tests. Adequate power was not obtained for the available sample (19 participants). For the various effect sizes and analyses for the hypotheses, power levels with a medium effect size ranged from 0.14 - 0.32, meaning that given a medium effect size, there would be only a 14-32% chance of rejecting a false null hypothesis. Since power levels of 0.80 and higher are considered adequate to find statistically significant results, the available power for this study‟s available sample was much lower than desired. In order to obtain adequate power (0.80) with a medium effect size, the necessary sample size would be $N = 34$. Therefore, qualitative analyses were conducted in addition to statistical analyses (*t*-tests) to provide a clearer picture of the data and its trends.

Main Analyses

For each hypothesis, several types of analyses were conducted. First, quantitative analyses were conducted for each hypothesis. Next, qualitative analyses for each hypothesis were conducted as well, given concerns about power levels. Supplemental post-hoc analyses were warranted and conducted for hypotheses 1A, 1B, and 3. The

analyses will be presented in the following order: Quantitative analyses, qualitative analyses, supplemental analyses.

Quantitative Analyses.

Hypothesis 1a.

It is expected that, when compared to overall cognitive functioning as measured by psychometric intelligence, survivors of Acute Lymphoblastic Leukemia (ALL) will demonstrate significantly impaired working memory functioning.

A paired-sample *t*-test was conducted to determine whether the Working Memory Composite (WMC) was significantly lower than the Full Scale IQ (FSIQ) for this sample. There was no significant difference in scores between FSIQ (M = 0.4279, SD = 1.0658) and WMC (M =-0.0879, SD = 1.7123; t (18) = 1.719, p = 0.103 (two-tailed)). However, the magnitude of the differences in the means (mean difference = 0.51582, 95% CI: -.11 to 1.15) was large (eta squared = 0.141).

Hypothesis 1b.

It is expected that, when compared to a normative sample, survivors of Acute Lymphoblastic Leukemia (ALL) will demonstrate significantly impaired working memory functioning.

A paired-sample *t*-test was conducted to determine whether the Working Memory Composite (WMC) was significantly lower than the mean Full Scale IQ (FSIQ) for the general population. The difference in scores between FSIQ (M = 0, SD = 0) and WMC

(M =-0.0879, SD = 1.7123; t (18) = 0.224, p = 0.825 (two-tailed)) was not significant. Additionally, the magnitude of the differences in the means (mean difference = 0.0879, 95% CI: -0.74 to 0.91) was small (eta squared = 0.0028).

Hypothesis 2.

It is expected that females will perform significantly worse on measures of working memory than males.

Given the abnormal distribution of males and females in the sample, *t*–tests could not be calculated for this hypothesis. In lieu of an independent sample *t*-test, the Mann-Whitney *U* test (a non-parametric test of differences between two independent groups on a continuous measure) was calculated. A Mann-Whitney *U* test revealed no significant difference in the Working Memory Composites (WMC) between males (Md = -0.19, n = 14) and females (Md = -0.76, n = 5; U = 29, z = -0.556, p = 0.578). The effect size (r = 0.1276) was small.

Hypothesis 3.

It is expected that, in survivors of Acute Lymphoblastic Leukemia (ALL), nonverbal working memory performance will be significantly worse than verbal working memory performance.

A paired-sample *t*-test was conducted to determine whether the Verbal Working Memory Composite (VWMC) was significantly lower than the Nonverbal Working Memory Composite (NVWMC) for this sample. There was no significant difference in

scores between VWMC (*M* = -0.2111, *SD* = 2.3691) and NVWMC (*M* = 0.1584, *SD* =0.7646; *t* (18) = -0.757, *p* = 0.459 (two-tailed)). The effect size of the differences in the means (mean difference = -0.3695, 95% CI: -0.37 to 0.66) was small (eta squared = 0.03). In addition, the relationship between verbal and nonverbal WMC was the opposite of the relation hypothesized, as the nonverbal composite was higher than the verbal composite.

Qualitative Analyses.

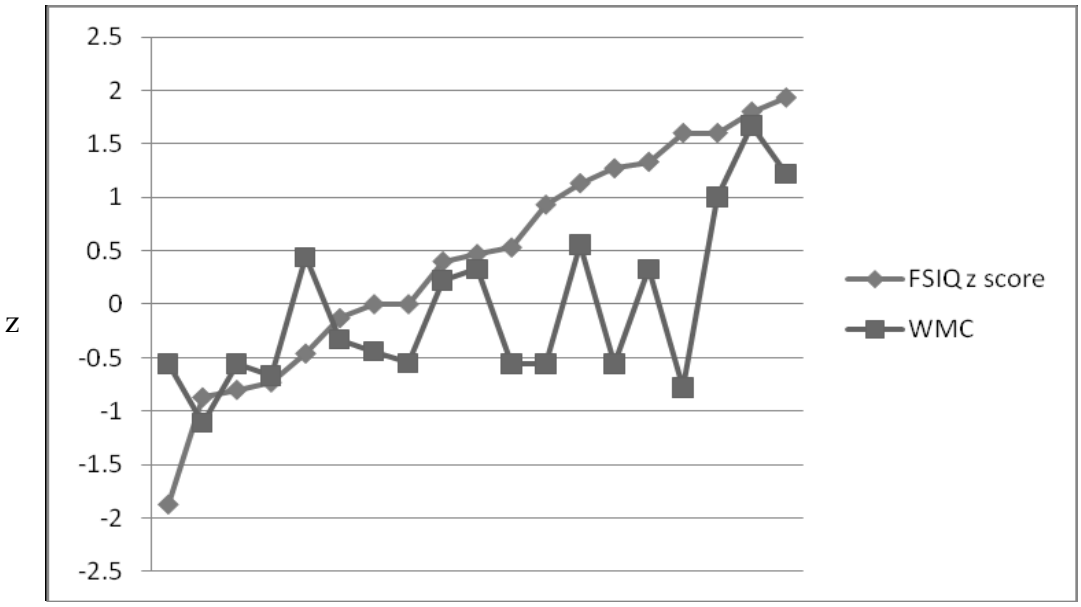
Hypothesis 1a: Working memory compared to sample IQ.

Qualitative analysis for Hypothesis 1a was tested by comparing each individual‟s Working Memory Composite (WMC) score to his or her Full Scale IQ (FSIQ) as determined by the Wechsler Abbreviated Scale of Intelligence (WASI). Each individual‟s difference score between FSIQ and WMC was computed, and a difference score of z =-1.0, or WMC being one standard deviation below FSIQ, was considered clinically significant. The value 1.0 was chosen as the significant value because a difference of this size would be considered significant in the clinical setting. If a child‟s working memory skills are 1 *SD* below his or her overall cognitive functioning, it would be considered a personal weakness.

The overall mean difference between the participants‟ FSIQ and WMC was *z* = 0.4758, which is not clinically significant. However, upon individual analysis, 6 of 19 participants displayed significantly lower WMCs than FSIQ, and 15 participants‟ WMC was below their FSIQ. The greatest difference between WMC and FSIQ was *z* = -2.38.

Figure 1 shows each participant‟s WMC and FSIQ comparisons, displaying how the majority of WMC scores were below FSIQ. While qualitative analyses did not produce clinically significant outcomes for hypothesis 1a, the results were in the expected direction.

Figure 1: FSIQ versus WMC



Subjects; $N = 19$

Hypothesis 1b: Working memory compared to population IQ.

Qualitative analysis for hypothesis 1b was tested by comparing each individual‟s Working Memory Composite (WMC) to the normative Full Scale IQ (FSIQ) mean of z = 0. The overall mean difference between the normative mean FSIQ and WMC was $z = -.479$, which is not clinically significant. Upon individual analysis, only 1 of 19 comparisons indicated significantly lower WMCs than FSIQ, and 11 participants‟ WMC

was below normative mean FSIQ. The greatest difference was z = -1.11. While qualitative analyses do not produce clinically significant outcomes for hypothesis 1b, again, the results were in the expected direction.

Hypothesis 2: Gender differences.

Hypothesis 2 was tested by comparing the Working Memory Composites (WMC) of male participants to the WMCs of female participants. Again, z = 1.0 was chosen as the significant value because a difference of this size would be considered significant in the clinical setting. The mean difference between male and female WMC was z = 0.1494, which is not significant.

Hypothesis 3: Verbal versus nonverbal working memory.

Hypothesis 3 was tested by comparing the mean Verbal Working Memory Composite (VWMC) to the mean Nonverbal Working Memory Composite (NVWMC). A difference score of greater than z = 1.0 was considered clinically significant.

The overall difference between the VWMC and NVWMC was z = 0.2742, which is not clinically significant. Additionally, the mean NVWMC was positive and the mean VWMC was negative, which was the reverse of what was expected.

Supplemental Analyses.

According to Reynolds (1997), composite scores may mask the effects of the individual scales that comprise a composite score. To investigate whether the Working Memory Composite (WMC) and Verbal Working Memory Composite (VWMC) were

accurate representations of the subscales that comprise them, post-hoc analyses were conducted using measures individually instead of the composite.

Hypothesis 1a: Working memory compared to sample IQ.

In addition to the paired-sample *t*-test comparing the Working Memory Composite (WMC) to Full Scale IQ (FSIQ), each subtest contributing to the WMC was also compared to the sample‟s FSIQ. A paired-samples *t*-test was conducted to compare the Digit Span Backward process scores to the FSIQ. There was a significant difference between the two scores (Digit Span Backward: M = -0.4221, SD = 0.8159; t (18) = 3.173, p = 0.005 (two-tailed)). The paired samples *t*-test comparing FSIQ to Visual Sequential Memory was not significant (Visual Sequential Memory (M = 0.1584, SD = 0.7646; t (18) = 1.225, p = 0.236 (two-tailed)). There was no significant difference in scores when comparing the FSIQ to Letters Backward (Log10 transformation; Letters Backward Log10: M = -0.0001 , SD = ;4.3594 t (18) = 0.493, p = 0.628 (two-tailed)).

Hypothesis 1b: Working memory compared to population IQ.

Individual paired-sample *t*-tests were run comparing each individual Working Memory Composite (WMC) subtest to the population Full Scale IQ (FSIQ) of z = 0. A paired-samples *t*-test was conducted to compare the Digit Span Backward process scores to the population FSIQ. There was a significant difference between the two scores (t (18) = 2.255, p = 0.037 (two-tailed)). The paired samples *t*-test comparing FSIQ to Visual Sequential Memory was not significant (Visual Sequential Memory (t (18) = -0.903, p =

0.378 (two-tailed)). There was no significant difference in scores when comparing the FSIQ to Letters Backward (t (18) = 0.000, p = 1.000 (two-tailed)).

Hypothesis 3: Verbal versus nonverbal working memory.

Individual paired-sample *t*-tests were run comparing each individual Verbal Working Memory Composite (VWMC) subtests to the Nonverbal Working Memory Composite (NVWMC; comprised of a single score: Visual Sequential Memory). A paired-samples *t*-test was conducted to compare the Digit Span Backward (DSB) process score to the NVWMC score. There was a significant difference between the two scores (t (18) = -2.762, p = 0.013 (two-tailed)) with DSB being significantly lower than VSM. The paired samples *t*-test comparing Letters Backward (with Log10 transformation; LB) to VSM was not significant ((t (18) = 0.117, p = 0.908 (two-tailed)).

Summary

Hypothesis 1a, which predicted that the sample‟s working memory would be below the sample‟s IQ was not confirmed with either quantitative (*t*-test) or qualitative methods. Upon supplemental analysis, the individual subtest Digit Span Backwards (DSB) was found to be significantly lower than the sample‟s IQ, but the other working memory subtests, Letters Backward (LB) and Visual Sequential Memory (VSM) were not significantly below IQ. Hypothesis 1b predicted that the sample‟s working memory would be below the population‟s mean IQ. Like hypothesis 1a, neither quantitative nor qualitative analyses yielded significant results, but supplemental analyses revealed that DSB was significantly below the population‟s IQ (neither LB or VSM were significantly

below IQ). Hypothesis 2 predicted that females would perform worse than males on measures of working memory. This hypothesis was not confirmed with quantitative or qualitative methods. Lastly, hypothesis 3, which expected that within the sample, nonverbal working memory would be significantly worse than verbal working memory, was not confirmed by either quantitative or qualitative methods. Additionally, upon supplementary analysis, DSB was found to be significantly below VSM, the nonverbal working memory subtest, and LB was not significantly different from VSM. The results of analysis for hypothesis 3 were in the direction opposite of what was expected.

Chapter V: Discussion

This study aimed to expand the research base for working memory late effects in survivors of pediatric Acute Lymphoblastic Leukemia (ALL), an understudied area in cancer survivorship. Working memory is an important cognitive ability that is heavily involved in the successful performance of many academic and daily-living activities. Specifically, this study investigated working memory ability in survivors of ALL as compared to overall cognitive ability, the effect of gender on working memory, and differences between verbal and nonverbal working memory. It was expected that, in survivors of ALL, working memory would be less developed than overall cognitive functioning, that females would perform worse than males on measures of working memory, and that nonverbal working memory would be less developed than verbal working memory. These hypotheses were generated based on previous research that confirmed the existence of attention and memory deficits, poorer female performance, and poorer performance on nonverbal tasks in survivors of ALL. Results for all tests of the current data were nonsignificant, indicating that working memory and overall cognitive ability were comparable, as was performance between males and females, and performance between verbal and nonverbal working memory tasks. However, supplemental analyses revealed an interesting and significant finding, that performance on the specific working memory subtest Digit Span Backward (DSB), a verbal working memory task, was significantly lower than overall cognitive ability and nonverbal working memory. The largely nonsignificant findings and the meaning of this important finding are next explored.

Nonsignificant Findings

In this study, none of the hypotheses were confirmed as all main analyses resulted in nonsignificant results. An obvious explanation for these results may be that working memory is not impaired in survivors of ALL who were treated solely with chemotherapy. This explanation goes against the previous literature that cites the importance of attention and memory in the successful utilization of working memory and cancer literature that confirms late effects in attention and memory, even in individuals treated with chemotherapy alone. So how could this be?

One potential explanation for the nonsignificant results is that, since ALL is typically diagnosed at a very young age (~ 3 years), the brain develops in a way that is resilient and spares working memory. Since development of higher order executive functions does not occur until later in childhood (~7 years), the young brain that is affected by treatment for cancer may develop atypical pathways that nevertheless result in intact working memory skills.

Another explanation may be that, since working memory is not governed by a single brain structure, but rather by multiple structures and pathways, damage done by chemotherapy may not be significant enough to disrupt the entire system of working memory. While memory and attention are frequently damaged in survivors of ALL, it may be that the damage to these two components of working memory is not enough to impart detrimental effects on the working memory system.

While the lack of significant findings does not lead to an interesting discussion of results, it would be a reason for celebration if working memory were truly spared in

survivors of ALL. However, this conclusion may be premature and studies investigating working memory in survivors of ALL treated with chemotherapy alone should not yet be dismissed. Supplemental analyses highlighting the importance of a specific working memory test and methodological limitations of this particular study are discussed next, as they give reason to continue studying this important cognitive ability in chemotherapy-treated survivors of ALL.

Working Memory in Survivors of ALL

Recent treatments for ALL have proven to be very effective at eliminating cancer, but they leave behind a variety of detrimental effects, many of which manifest long after treatment is terminated. These "late effects" of treatment have been found to have an influence on many areas of cognition, including memory and attention, which in turn negatively impact academic and daily-living skills. This study focused on working memory (which relies heavily on both attention and memory and is essential in the successful performance of many tasks), asking the question as to whether it is actually impaired in survivors of Acute Lymphoblastic Leukemia (ALL). In an attempt to answer this question, working memory skills were compared to overall cognitive functioning (IQ), to determine if the ability was specifically impaired. Reasonable estimates of working memory and IQ were obtained. As determined by main qualitative and quantitative analyses, no significant differences between working memory and IQ were found. However, in performing specific supplemental analyses and looking at effect size and directionality of results, a more complex understanding of the findings was revealed.

The main analyses used a working memory composite (WMC) to estimate working memory ability, which was the average of performance on three individual tasks measuring working memory. Using the WMC, no significant differences were found between working memory and the sample or population IQ. Likewise, when using a verbal working memory composite (VWMC) compared to a nonverbal working memory task (Nonverbal Working Memory Composite, NVWMC), no significant differences were found. These results were unexpected, but in working to better understand the nature of composites, it was learned that composite scores, such as the ones used for this study, may "wash out" the effects of the individual scores that comprise them (Reynolds, 1997). Therefore, supplemental analyses were conducted to determine if individual differences between task and IQ (Hypothesis 1a and 1b) and verbal and nonverbal working memory tasks (Hypothesis 3) existed.

Among the subtests comprising the WMC, one stood out in supplemental analyses: Digit Span Backward from the Wechsler Intelligence Scale for Children, Fourth Edition (DSB; WISC-IV; Wechsler, 2003). DSB was significantly lower than the sample‟s IQ, the population‟s IQ, and the Visual Sequential Memory subtest from the Test of Memory and Learning, Second Edition (VSM; TOMAL-2; Reynolds & Voress, 2007). When compared outside of the composite, performance on this subtest (DSB), which represents the most commonly used type of working memory task in evaluations (Ackerman et al., 2005), was significantly lower than cognitive and other working memory performance. This appears to be a unique finding to this study, as it does not appear elsewhere in the literature, and warrants further investigation.

An interesting question is: Why is Digit Span Backward so different? What is it about this particular task that makes it significantly more difficult than other working memory tasks? When the working memory tasks from the TOMAL-2, Letters Backward (LB) and VSM, were compared to IQ, there were no significant differences, indicating a potential difference in either the task of DSB, or possibly the norms from which scores are derived.

As DSB and LB are compared, the main distinction appears to be the difference between having to listen to numbers and then repeat them in reverse order (DSB) versus listening to letters and repeating them in reverse order (LB). While the examinee is required to perform very similar tasks on these subtests, the methods of scoring the items are different. DSB requires the examinee to repeat all digits in the reverse order to receive credit, whereas LB accepts all letters that are recited in the proper place as correct. For example, on DSB, if an individual switches the location of two numbers in a response, the entire response is incorrect, even if all other numbers are correctly located. On LB, if an individual makes the error of switching two letters in a response but all other letters are in the proper place, partial credit for the item is given. Therefore, if an individual responds with inaccurate manipulation of information, decay of information, or both, he may still earn credit on LB, but not on DSB.

When comparing DSB to VSM, there are many observable differences, as DSB is a verbal working memory task whereas VSM is a visual working memory task. DSB requires the examinee to listen to the stimuli and then manipulate it without any aids (e.g. visual aid, repetition). VSM, on the other hand, requires the examinee to view several

designs in a particular order, then look at the same designs in a different order. The initial stimuli are shown twice, removing some exertion on the immediate memory. The examinee must then point to the designs in the order initially presented. Like LB, VSM allows credit on all correctly sequenced stimuli, so the examinee need not display perfect performance on items to receive credit. Face value of comparing these tasks indicates that DSB may place more strain on the working memory system than VSM because DSB requires both complete and accurate memory of the stimuli and precise manipulation. While VSM also requires memory of the stimuli, the stimuli is re-introduced during each item, potentially allowing a memory boost for decayed information and total accuracy is not essential for item credit.

Thus, when comparing DSB to both LB and VSM, DSB may impart the greatest load on working memory. Both LB and VSM allow room for error and VSM also provides re-introduction of the stimuli. These differences may account for DSB scores being significantly lower than IQ and visual working memory. When approached with the understanding that DSB may be a more stringent and pure estimate of working memory, it provides support for the notion that working memory may be impaired in this study"s population (survivors of pediatric ALL).

Since DSB is a subtest from the WISC-IV and LB and VSM are subtests from the TOMAL-2, a comparison of norms and reliability must also be considered. The normative sample of the WISC-IV is slightly greater than that of the TOMAL-2, with 2200 individuals from all states in the United States compared to 1961 individuals from only 28 states. However, both manuals state that the sample"s gender, race,

socioeconomic status, parent level of education, geographic region, exceptionality status, and age were effectively correlated with the US census data, indicating a representative sample (Reynolds & Voress, 2007; Wechsler, 2003). Additionally, reliability estimates for all three subtests were strong. Therefore, the difference in DSB is not likely contributable to differences in norms or reliability.

In addition to comparing working memory to overall cognitive abilities, this study also aimed to compare verbal and nonverbal working memory, expecting nonverbal memory to be less well developed. As mentioned previously, supplemental analyses revealed that performance on Digit Span Backward (DSB) was significantly lower than Visual Sequential Memory (VSM). This pattern of performance is the opposite of what was expected, given that DSB is a verbal task and VSM is a nonverbal task. This unexpected finding is unique to this study and has not been found or investigated elsewhere and could be a result of several different explanations. This finding may reflect a true difference between verbal and nonverbal working memory in survivors of ALL. If this reason holds, it may be that nonverbal working memory differs from other nonverbal tasks in survivors of ALL in such a way that nonverbal working memory is unimpaired by late effects. Another possibility is that this pattern of working memory functioning holds in the general population and is non-specific to survivors of ALL, indicating no unique working memory problems in the study‟s population. A third consideration, as previously discussed, is that this finding may be a reflection of measurement issues within the study as DSB, the verbal working memory task, was a more sensitive measure

of working memory. While this hypothesis resulted in unexpected findings, the overall significance of DSB links with previous research in several areas.

If working memory is indeed part of the myriad of late effects that are found in survivors of ALL, previous research would support this finding in several ways. First, if working memory is impaired in survivors of ALL, even to a slight degree, it would align with previous literature in several areas. This finding is consistent with literature indicating that white matter damage, particularly in the right prefrontal cortex, may be the mechanism responsible for many cognitive late effects (Carey et al., 2008; Reddick et al., 2006). Since individuals exposed to chemotherapy lose white matter, particularly in the brain region responsible for many executive functions, it makes sense that working memory, a complex and integrative skill that is important to executive function, could potentially become impaired.

Negatively affected working memory is also consistent with models of working memory that purport the importance of memory and attention. Since memory and attention have been shown to be very sensitive to late effects (e.g. Ashford et al., 2010; Askins & Moore, 2008; Reddick et al., 2006; Spencer, 2006) and are vital to working memory performance (Baddeley et al., 1984; Baddeley & Hitch, 1994; Bishop & Robson, 1989), the finding of poor Digit Span Backward performance is consistent with this literature and model.

Poor performance on DSB is also consistent with previous research that indicates specific deficits in mathematics (Brown et al., 1992). The skills required to perform well on DSB are very similar to the skills required to perform mental mathematics; both

require accurate mental manipulation of numbers. Previous research confirms working memory‟s importance in mathematics (Adams & Hitch, 1997; Gruber et al., 2001). This strong link between working memory and mathematics implies that survivors of ALL may benefit from specific modifications, particularly in the area of mathematics, to perform at age and grade expected levels.

In summary, Digit Span Backward (DSB) was significantly impaired whereas other working memory tests were not impaired in survivors of ALL treated with chemotherapy alone. Upon examination of the individual working memory tasks, DSB was found to be unique in several ways, and was determined to be the most sensitive and "pure" measure of working memory. Working memory is understudied in pediatric cancer survivorship literature and has not yet been identified as an area impacted by late effects of treatment. However, this unique finding that DSB is significantly lower than IQ and other working memory tasks implies that, in contrast of nonsignificant results of main analyses in this study, working memory, as measured by a sensitive test, may be an important part of the constellation of late effects that affect survivors of ALL.

Effect Size and Trends of Working Memory Performance

Effect size and directionality of data were considered in addition to formal hypothesis testing to contribute additional understanding of the data. Effect size is another way to quantify the extent of the difference between groups (Urdan, 2010). The effect size essentially estimates the magnitude of the relationship, independent from determining if the mean differences are great enough to be significant (*t*-tests in this study). It was hypothesized that working memory ability would be significantly below

the IQ in survivors of pediatric ALL (Hypothesis 1a), and while statistical significance was not found, the effect size was large. This large effect size provides evidence in support of the hypothesis that working memory is impaired in survivors of ALL.

Although qualitative and quantitative analyses did not confirm a significant difference between working memory and sample IQ, the large effect size confirmed that there was, indeed, a strong relationship between working memory and IQ.

In contrast, when working memory was compared to the population‟s IQ (Hypothesis 1B), the effect size was small, indicating a weak relationship between working memory and population IQ. The difference in the effect sizes between these two hypotheses (1a: working memory versus sample IQ; 1b: working memory versus population IQ) may be explained by the finding that, in the sample population, IQ was four standard score points higher than the overall population IQ (Sample IQ: 104; Population IQ: 100). Therefore, when comparing the same estimate of working memory, the difference between working memory and the sample IQ was larger than the difference between working memory and the population IQ.

As stated previously, the difference between working memory and IQ in this population was not great enough to yield statistical significance. Qualitative methods did not produce evidence of clinical significance either. However, upon further examination of qualitative data, an interesting clinical picture appeared. Most participants‟ working memory performance was lower than his or her IQ (15 of 19; 79% of participants) and over half of the sample‟s working memory performance was lower than the sample IQ (11 of 19; 58%). Although working memory was not a glaring deficit, the trend of

poorer performance on working memory tasks than on other cognitive tasks, particularly among intraindividual comparisons, held across most participants. This pattern may indicate milder deficits in working memory that could nevertheless impact functioning. For instance, parents or teachers may expect a child who displays above average overall intelligence to be able to keep up with difficult mental arithmetic and orally-administered directions. However, if the child has even mild working memory problems, he or she may not be able to perform as well on working-memory heavy tasks. In this way, even though the deficit is small, it may have functional implications.

The findings of poorer performance on DSB and the large effect size between working memory and IQ provide evidence in support of the value of continued research and investigation of working memory in survivors of ALL. Additionally, the limitations of this particular study are vital to review, as the results must be understood within the context of the study"s restrictions.

Nonsignificant Effect of Gender

In addition to investigating the effects of working memory for the entire sample, gender was independently analyzed. Literature in late effects has reported that overall, female pediatric cancer survivors tend to exhibit more exaggerated late effects than their male counterparts (Peterson et al., 2008). Thus, it was hypothesized that this pattern would hold true for this study"s population when comparing working memory ability. However, analysis from this study indicated that no gender differences existed for the sample. It is possible that the disproportionate number of males to females may have hindered the ability to detect differences, as males outnumbered females at nearly a 3:1

rate (14 males, 5 females). It is also possible that working memory is neither impaired nor different between male and female survivors of ALL treated with chemotherapy.

Limitations

Given the available sample and resources, there are several important limitations of this study. As previously addressed, the sample size was small which led to decreased power to find significant differences in addition to restricted methods of statistical analysis. This is an important limitation to understand, as it affected the effectiveness of statistical analyses to provide accurate information about the "true" nature of the sample. As such, the statistical results of this study do need to be interpreted with caution and would be best if re-analyzed with a larger sample.

The sample"s composition was limited by several restrictions. It was restricted ethnically, as it represented only two ethnic groups (Caucasian, Latino). There was also a significantly uneven distribution of males and females which was not consistent with ALL or general population estimates. Since the sample is not matched to ALL survivor population or general population, it is much more difficult to make generalizations. The data from this study also represent a single point in time, making baseline and longitudinal comparisons impossible. That is to say, while statistically significant deficits in working memory were not present at the time of testing for this study, there may have been a change in skills present before treatment that could not be detected using a single data point.

Additionally, as discussed earlier, the measure used for visual working memory (Visual Sequential Memory) may not have accurately measured nonverbal working

memory. The design of the subtest allows the examinee the advantages of (1) seeing the stimuli multiple times and (2) allowing for some response error. A recommended beneficial, albeit difficult, task for test development may be the creation of a task that more purely measures visual working memory.

These limitations raise questions about accuracy and generalizability of the results of this study. The nonsignificant results may reflect a true absence of working memory problems in this sample, but the restriction of available data may also have hindered the analyses‟ ability to detect accurate results.

Implications

While this study purported several hypotheses, none of them resulted in significant outcomes. It is important to acknowledge that one explanation for these nonsignificant results across hypotheses may well be that survivors of ALL do not suffer from late effects in the area of working memory. However, this does not imply that research in this area should cease. Conversely, implications for future research and clinical care are discussed in light of the limits of this particular study.

As is true for most studies, a large sample size is ideal, and future studies should obtain the largest *N* possible. A major benefit of a large sample size is the increased power to find significance. Although ALL is the most commonly diagnosed malignancy in childhood, it is still fairly rare amongst the general population, and therefore, a large sample size may be well acquired through a multisite study. This larger *N* should better represent the general population with a more balanced representation of ethnicity, gender,

socioeconomic status, geographic location, and other population characteristics to allow for generalization of results.

The addition of a control group is another way to strengthen future research. For this study, a control group would have allowed for between-group comparisons to be conducted. These comparisons between IQ and working memory in both survivors and typical children could better allow determination of whether any significant findings are unique to the ALL population. Additionally, differences between overall cognitive functioning between groups could be tested to determine if any differences were present. Future studies should aim to include a control group whenever possible.

In this study, since the participant‟s IQ and working memory were measured once, it is unclear whether any deficits or strengths were present before treatment for ALL began. Unfortunately, much of the ALL research has been conducted in a similar fashion. Since late effects, by their nature, occur after completion of treatment, an estimate of premorbid functioning (baseline testing) would provide valuable information. Additionally, multiple points of data throughout survivorship, or serial evaluations, would be beneficial as they would allow for any patterns of loss of functioning over time to be studied. It would be worthwhile for future studies to have baseline testing and at least one data point during survivorship, if not more. Fortunately, given the increased knowledge of cognitive late effects, many hospitals and clinics are now recommending that a baseline neuropsychological evaluation be conducted prior to the completion of treatment for ALL. Additionally, follow-up evaluations throughout survivorship are becoming more commonplace.

Future research might create models of hypothesis testing that allow for comparisons between different treatments types and intensities to determine whether specific treatments affect working memory in different ways. This study did not account for differences in intensity of treatment due to the study design and small available sample. Although this study"s sample was comprised of similar participants, in that they all received only chemotherapy during treatment and had no recurrence of cancer, there were differences in the types and intensity of treatment received, which were not accounted for.

The unexpected finding that verbal memory was better developed than nonverbal memory implies that a more "pure" measure of visual working memory that allows for visual stimuli to only be present once may need to be created and utilized to truly measure nonverbal working memory. An additional implication is that the relationship between verbal and nonverbal working memory should continue to be studied in future research to better understand the nature of these differences.

Although the results of this study are limited, implications can be gleaned from this research, most of which pertain to research conducted in the future. While results of main analyses were nonsignificant, the fact that Digit Span Backward (DSB) was significant across hypotheses does suggest that working memory may indeed be negatively impacted in survivors of pediatric ALL. Importantly, amongst the measures of working memory assessed, DSB appears to have been the most sensitive, stringent and pure measure of working memory.

The results of this study may impact the various professionals that work with survivors of ALL if working memory is damaged. First, clinicians should know that working memory may be negatively impacted in this population. They should understand that working memory is essential for academic achievement (mathematics in particular), other academic activities such as note-taking, and daily-living skills, such as properly sequencing and carrying out daily routines. Clinicians should also appreciate the need for baseline and follow-up evaluations and heed the importance of making recommendations specific to working memory deficits if they are present for an individual.

Second, individuals who interact with survivors of ALL on a daily basis, such as parents and teachers, should be provided with psychoeducation on how to identify if working memory is impaired, how working memory and other cognitive deficits may manifest, what life areas may be affected, and how they can support the needs of these individuals in regards to working memory deficits, in combination with other potential cognitive deficits. This way, for individuals who may have deficits in working memory, even if they are slight, can be identified and supported.

Finally, the results of this study have implications for research, not only in social science, but medical science as well. As outlined earlier, social science researchers should continue to study working memory in survivors of ALL with greater, more representative samples and more complex statistical methods. Medical researchers should continue to try to refine the balance between treatment that increases survivorship while reducing the quantity of neurotoxic agents (and possible late effects) given to individuals with ALL.

Conclusions

The primary goal of this study was to investigate working memory ability in survivors of pediatric Acute Lymphoblastic Leukemia (ALL) who were treated with chemotherapy only. Survivors‟ working memory, as compared to overall cognitive functioning, was explored in addition to comparisons between verbal and nonverbal working memory and gender comparisons. While the main analyses were nonsignificant, the findings of this study nevertheless have implications for continued research and potentially disease treatment, assessment, and intervention of survivors of pediatric ALL in the future.

Many results of this study were nonsignificant, which may be due to a lack of working memory deficits in survivors of ALL, or it may be attributed to methodological issues. Regardless of the cause of these nonsignificant outcomes, future research is implicated to determine whether or not deficits truly exist. If future research mirrors the nonsignificant findings of this study, the results would be a cause for celebration amongst survivors of ALL. An important executive cognitive skill would be intact and a research base for resiliency in survivors of ALL treated with chemotherapy alone could begin. Conversely, if future studies that implement stronger methodology find that there are impairments in working memory, then it will have implications for future identification and treatment of affected individuals. Therefore, working memory in survivors of ALL treated with chemotherapy only should continue to be examined in future research with larger samples, control group comparisons, baseline data, and multiple time point comparisons.

The interesting finding that Digit Span Backward (DSB) from the WISC-IV was impaired when compared to other scales in this study may imply that impairments do exist on a more sensitive measure of working memory. Since deficits in working memory are linked to academic achievement, classroom performance, and daily functioning, this finding needs to be considered as individuals in this population may require specific modifications and interventions should a deficit in working memory be present. Implications of this finding may affect clinicians, parents, teachers, and social and medical science researchers.

Overall, this study produced one of the first looks at working memory in survivors of pediatric ALL treated solely with chemotherapy and results highlighted potential deficits or absence of deficits in working memory in this population. The findings of this study support the need for continued research in working memory in survivors of ALL to best understand and subsequently intervene with any potential deficits.

Appendix A
Consent Form

Parent/Guardian Informed Consent Agreement

Please read this consent agreement carefully before you decide to allow your child to participate in this research study. Your child will also receive an assent form; please review the assent form with your child.

Hello,

On behalf of the University Of Texas at Austin and the LIVESTRONG Survivorship Center at *Dell Children's Blood & Cancer Program of Central Texas* we are inviting you to participate in a potentially important research study. Our names are Daniel Garrison and Amanda Winter and we are doctoral students in School Psychology (Educational Psychology Department) at the University of Texas at Austin. The purpose of this study is to investigate the potential long-term effects of cancer treatments in survivors of childhood ALL. This study is part of our doctoral dissertations and will potentially lead to a better understanding of the effects of treatment toxicity on the brain. Specifically, we will be looking at the following abilities: working memory (the ability to manipulate information in memory), processing speed (the ability to efficiently process information), and executive function (the ability to plan, organize, monitor, and self-regulate one's actions to achieve a goal).

In order to gather this information from these specific abilities, your child we be asked to complete a full neuropsychological assessment that consists of various tests that provide information on how to solve problems with and without using your words. Many children find these tests to be interesting and even fun and will provide information on how he/she thinks and learns. Testing will require approximately 150 minutes of your child's time and effort. This testing will take place in a quiet room at Dell Children's Blood and Cancer Program of Central Texas. Your child may take a break at any point during the evaluation.

As your child completes the assessment, you will be asked to fill out a brief history form and questionnaire requiring approximately 30 minutes of your time. In addition, you will given a separate, brief questionnaire and a self-addressed, stamped envelope, to give to your child's teacher to complete and return.

Upon completion of the assessment, we will score and interpret the results and provide you with a comprehensive, integrated report, which you may use as you wish. Some parents use such a report to assist in the development of any needed educational planning or interventions. We are available to give you feedback over the phone

regarding the results and any of their implications. The neuropsychological assessment, report, and feedback will be provided at no charge. Each assessment will be supervised by Rachel Robillard, Ph.D., L.S.S.P.(Credentialed Psychologist, Seton Healthcare Systems).

Please read the following carefully and thank you in advance for your consideration in participating in our study.

Sincerely,

Daniel A. Garrison, M.A.

Doctoral Candidate

The University of Texas at Austin

School Psychology

Educational Psychology

Telephone: (512) 773-1267

Amanda L. Winter, M.A.

Doctoral Candidate

The University of Texas at Austin

School Psychology

Educational Psychology

Telephone: (512)-917-0766

Purpose of the research study: The purpose of this study is to examine working memory, speed of information processing, and executive function in survivors of childhood ALL. These abilities have implications for a child's educational, social, emotional, and daily functioning. This investigation also aims to investigate risk factors that may make it more likely to develop such problems in the future. Examples of potential risk factors include intensity of treatment, age at diagnosis, and gender.

What will you and your child do in the study: If you and your child consent to participate in this investigation, you will be asked to attend a single assessment session at *Children's Blood & Cancer Program Dell Children's Medical Center of Central Texas* in Austin, TX. At that time, your child will complete a neuropsychological evaluation that will take approximately 150 minutes. You, as the parent/guardian, will be asked to complete two additional surveys that will take approximately 30 minutes total. If you also consent to and sign an "Exchange of Information" form, one of your child's teachers will be sent a similar survey that will ask him or her to answer questions regarding your child's neurocognitive functioning in the school system. This survey will take approximately 30 minutes for your child's teacher to complete and you will be provided with a self-addressed stamped envelope to be used in returning the teacher survey through U.S. Mail.

The performance on neuropsychological tasks, answers to all surveys, as well as any demographic information that is collected, will be used to determine any problematic long-term effects that pediatric cancer survivors may or may not experience that may be associated to their completed treatment. This study will also require our access to your child's cancer treatment summary in their medical history. We will only be looking at the date of diagnosis, date of last treatment, and the dosage of treatment received.

The primary investigators may also contact you to answer any questions or address any concerns you have. You are also encouraged to contact the investigator if you have any questions and/or concerns about you or your child's participation.

While it is important to receive all materials fully completed, you and your child may skip any question or stop any evaluation task that may make you or your child feel uncomfortable. You and your child may stop the any part of the evaluation at any time.

Confidentiality: All information attained in this study will be handled confidentially. Your information will be assigned a code number and the list connecting your child's name and/ or your name to this code will be kept in a locked file. When the study is completed, this list will be destroyed. Your child's name and/or your name will not be used in any report, other than the one provided to you upon completion of the assessment.

Researchers are required by Texas state law and professional ethics codes to report to Child Protective Services (or other appropriate regulatory agency) all instances of alleged child abuse and neglect. Please not that if your child is believed to be at risk for emotional, psychological or possible physical harm or neglect, then the investigator will report this information to the attending physician, Child Protective Services, and any other necessary regulatory agencies. Please note when a child reports neglect or being harmed, participants cannot stop the referral of their child's case to the authorities and any subsequent actions taken.

If you have any questions about the study, concerns, or to withdraw from the study, you can call Rachel Robillard, Ph.D. at (512)-934-7858 or you may contact one of us.

If you have questions about your rights as a participant, please contact Lisa Leiden, Ph.D., Chair, The University of Texas at Austin Institutional Review Board for the Protection of Human Subjects, (512)-471-8871.

If you consent to it below, the data resulting from your participation may be made available to other researchers in the future.

Time required: The forms included in a full neuropsychological assessment will require approximately 30 minutes of your time. Forms to be completed by your child's teacher will require approximately 30 minutes of their time. **Your child should expect to spend approximately 150 minutes to complete the neuropsychological assessment.**

Benefits: The study may provide beneficial information on the neuropsychological functioning of your child. You will receive a full neuropsychological evaluation and report, at no charge, that may be used to inform the development of any educational planning or interventions, if needed. The study may add to research on any long-term cognitive effects that pediatric ALL survivors may experience. In addition, results of this investigation may add to the development of future treatment protocols that reduce the likelihood of such problems as a result of treatment.

Risks: Anticipated risks in this study may include minimal psychological discomfort related to questions about current neurocognitive problems. Your child may also experience mild fatigue or frustration in response to the duration of the evaluation. Because some questions may be of a sensitive nature, you and your child are not required to answer those items. In the event that these questions produce psychological discomfort, you may have your concerns addressed and/or receive debriefing consultation by Dr. Rachel Robillard, Ph.D. (512- 934-7858) or Dr. Cindy Carlson, Ph.D., (512-471-0276) licensed psychologists and university faculty sponsors.

Voluntary participation: You and your child’s participation in this study (as well as the participation of your child’s teacher) are completely voluntary.

Right to withdraw from the study: You are free to refuse to be in this study. You are free to discontinue participation for any reason at any time, and your refusal or discontinuation will not influence current or future relationships with The University of Texas at Austin or Dell Children's Hospital.

Please check the appropriate box indicating that YES you have read this letter and are giving permission for you and your child to participate in this study or NO you do not want to participate. Regardless of your decision, please sign this form indicating your choice.

How to withdraw from the study: If you and/or your child want to withdraw from the study, tell the researcher. There is no penalty for withdrawing. If you would like to withdraw after your materials have been submitted, please contact the principal investigators, Daniel A. Garrison or Amanda L. Winter at austinoncology@gmail.com

Payment: You will receive no payment for participating in the study.

STATEMENT OF SUBJECT CONSENT

Do not sign this consent form after: *(_____)*

1. This study has been explained to me. I voluntarily agree to take part in this study. I have had the opportunity to ask questions. I understand that the investigators listed on this form can answer future questions I may have about this study and my child"s rights. By signing this form I understand that I am not giving up any of the patient rights listed on the attached "Patient Bill of Rights". I understand that signing this consent does not take the place of any other consent forms I have signed. I understand that I will be given a copy of this consent to keep and that if I request it, I will be given a copy of the study protocol.

- **YES** I give permission for my child, _____, and me to participate in this study. This includes permission for (1) my child to participate in the assessment, (2) permission for the researchers to access my child's cancer treatment history in his/her medical records, (3) permission for my child's teacher to complete a questionnaire regarding my child in the classroom, and (4) the data from this study to be used in future research.

- **NO** I do not give permission for my child, _____, and me to participate in this study.

_____ _____

Signature of Parent/Guardian Printed Name

_____ _____

Date Time

If you have questions about the study, contact the Principal Investigators:

Daniel A. Garrison
School Psychology Program
1 University Station D5800
Austin, TX 78712
Telephone: (512) 773-1267

Amanda L. Winter
School Psychology Program
1 University Station D5800
Austin, TX 78712
Telephone: (512)-917-0766

Faculty Advisors:

Rachel Robillard, Ph.D., LSSP
4810 B Spicewood Springs Rd.
Austin, TX 78759
robillard@alumni.utexas.net
Telephone: (512) 934-7858

Cindy Carlson, Ph.D, Professor
Department of Educational Psychology,
College of Education
1 University Station D5800
Austin, TX 78712
cindy.carlson@mail.utexas.edu
512-471-0276

If you have questions about your rights in the study, contact:

Sharon Horner, RN, PhD
Brackenridge Hospital"s IRB Chair
601 E 15th Street
Austin, Texas 78701
(512) 324-7991

Jody Jensen, Ph.D., Chair
The University of Texas at Austin
IRB for the Protection of Human Subjects
(512) 232-2685

The University of Texas at Austin
Office of Research Support
(512) 471-8871
email: orsc@uts.cc.utexas.edu

EXPERIMENTAL SUBJECTS BILL OF RIGHTS

What are your child's rights as a research subject?

The following is the *Experimental Subject's Bill of Rights*. Please read and keep this information for future reference. Although the principal investigators may be available to answer related questions, those pertaining to subject rights listed below should be addressed to the Chair of the Brackenridge Institutional Review Board, Sharon Horner, RN, PhD at (512) 324-7991.

1. To be told what the study is trying to find out.

2. To be told what will happen to your child and whether any of the procedures, drugs, or devices that are different from what would be used in regular practice.

3. To be told about the frequent and/or important risks, side effects or discomforts of the things that will happen to your child for research purposes.

4. To be told if your child can expect any benefit from participating and, if so, what the benefit might be.

5. To be told the other choices your child has and how they may be better or worse than being in the study.

6. To be allowed to ask questions about the study, both before agreeing to volunteer and during the study.

7. To be told what kind of medical treatment is available if your child has any problems.

8. To refuse to have your child participate at all or to change your mind about his/her participating after the study is started. This decision will not affect your child"s right to receive the care he/she would receive if he/she were not in the study.

9. To receive a copy of the consent form.

10. To be free of pressure when deciding whether you wish to allow your child to be in the study.

I have fully explained this clinical research study to the participants, and in my judgment, and theirs, there is sufficient information regarding the risks and benefits to make an informed decision. I will inform the participants in a timely manner, of any changes in the risks and benefits of this clinical research study.

_____	_____	_____	_____
Investigator Signature	Printed Name	Date	Time

Appendix B
Assent Form

Minor Informed Assent Agreement 13-17

Please read this assent agreement with your parent(s) or guardian(s) before you decide to participate in the study.

WHAT IS THIS INVESTIGATION ABOUT? Hello, our names are Daniel Garrison and Amanda Winter and we are graduate students in School Psychology at the University of Texas at Austin. We would like to tell you a little about our study. You may remember that when you were being treated for cancer, you may have sometimes experienced negative side effects of treatment such as hair loss, vomiting, loss of appetite, stomachaches, pains, etc.

You may also have experienced problems with your thinking, memory, concentration, balance, speech and vision problems. Fortunately, a lot of those effects went away when you finished treatment; for some, however, those side effects remain. Although we know a lot about the potential effects on the body caused by treatment, we still do not know a lot about how your experience and the treatments you received (like chemotherapy and/or radiation) affect thinking and memory in children and adolescents years later.

WHAT DO I HAVE TO DO? As part of our study, you will be asked to complete a neuropsychological assessment that will take approximately 150 minutes of your time. During the assessment, you will be asked to complete several problem-solving tasks using language, your memory, your ability to do things quickly, as well as your ability to figure out patterns and puzzles. Most people who complete an assessment find it to be an enjoyable experience. You can do it all at once, or you can take breaks and complete the assessment in chunks. We will also ask one of your parents, and one of your teachers to fill out some questionnaires about your thinking and feelings at home and at school.

RISKS AND BENEFITS: If you participate in the study, you may get tired and some of the tasks may seem sort of hard. You may take a break, or stop, at any time. You may also be uncomfortable if you are not used to answering questions about your emotions. However, if you get to a question and you do not want to answer it, you can skip it. If you start the assessment and realize you don't want to complete it, you can stop at any time with no penalty to you or your family. If you continue to experience discomfort, your parent/guardian can contact Dr. Rachel Robillard, Ph.D. (512- 934-7858) or Dr. Cindy Carlson, Ph.D., (512-471-0276) licensed psychologists and university faculty sponsors.

If you participate in this study, there will not be any direct benefit to you. You and your parents, however, will get a full report of how you did and what that means. If some things are harder for you now that you're done with treatment, it can help get you help you need. Your participation in this testing will help us better understand thinking, learning and memory in cancer survivors, which may help us prevent those problems from happening in children and adolescents who may be diagnosed with cancer in the future.

CONDIFENTIALITY: The information that you give to us during this study will be kept private. Your name will not be used.

DO I HAVE TO PARTICIPATE? You don't have to participate in this study and you can stop doing the study at any time. If you want to stop doing the study, tell your parents and one of us, Daniel Garrison or Amanda Winter. If you choose to stop before we are finished with the study, any testing you already did will be destroyed. There is no penalty for stopping. If you decide that you don't want your materials in the study but you already turned them in, contact Daniel Garrison or Amanda Winter at austinoncology@gmail.com.

Agreement: (Parents/Guardians: Please read aloud to your child if they are unable to read)

- I understand that my Mom, Dad or Guardian has said that it is okay for me take part in this study about the effects of my cancer treatment.
- I understand what this study is about.
- I understand that I am agreeing to complete an assessment that will last 150 minutes.
- I am going to be in this study because I want to.
- I have been told that I can stop being a part of this study anytime I want to. Nothing will happen to me if I want to stop.

_____ _____

Signature of Child Printed Name of Child

_____ _____

Signature of Parent/Guardian Printed Name of Parent/Guardian

_____

Date

Minor Informed Assent Agreement 6-12

Please read this paper with your Mom or Dad.

Hello, our names are Daniel Garrison and Amanda Winter and we are students at the University of Texas. We are working on a study to learn about kids like you who were treated for cancer. You probably remember that the medicine you took to fight the cancer had side effects that made you feel sick. Most of the these side effects go away when you stop treatment, but for some children, they may have other side effects on their thinking and memory, even though they have stopped treatment. For some kids, this can make learning harder once they return to school, even if the doctor has told them that their cancer is gone and that things are back to normal.

We don't really know if or why this might happen, but we would like to find out. If we find that kids like you are having a hard time with different ways of thinking and remembering things long after you finished treatment, then we and others can use that information to develop ways keep these things from happening at home and school.

As part of our study, we would like to ask you to complete a bunch of different activities, like puzzles and games. Most people who complete these activities usually say they have fun answering the different questions and trying the different activities and puzzles. It should take you about 2 and a half hours to complete, but you can always take breaks and come back to it later if you get tired.

RISKS/BENEFITS: It may seem like some of the activities we do are hard and like it is taking a long time. Also, some questions about problems might make you feel uncomfortable or sad. If you start to feel tired, sad or nervous during any activity, you can stop at any time and tell your parent or guardian. Answering these questions won't help you directly, but you and your family will learn a lot about how think and learn. Also, hopefully your answers will help us learn more about children and any problems with thinking or learning they might have after finishing treatment.

CONFIDENTIALITY: Your answers to our questions during this study will be kept private. Your name will not be used, and no one who reads about our study will know it was you.

Your answers to our questions during this study will not have your name on it, so we won't know what answers you give.

DO I HAVE TO PARTICIPATE IN THIS STUDY? You don't have to participate in this study. You can stop doing the study at any time. If you want to stop doing the study, you can tell your parents and they will tell us. If you choose to stop before we are finished

with this study, any answers you already gave will be destroyed. You will not get in trouble for stopping. If you decide that you don't want your materials in the study but you already turned them in, tell your parents to contact us.

Agreement: (Parents/Guardians: Please read aloud to your child if they are unable to read.)

- I understand that my Mom, Dad or Guardian has said that it is okay for me take part in this study about the effects of my cancer treatment.
- I understand what this study is about.
- I understand that I will be testing for 2 and a half hours.
- I am going to be in this study because I want to.
- I have been told that I can stop being a part of this study anytime I want to. Nothing will happen to me if I want to stop.

_____ _____

Signature of Child Printed Name of Child

_____ _____

Signature of Parent/Guardian Printed Name of Parent/Guardian

_____

Date

Appendix C

Descriptive Statistics of the Sample

Table 2

Descriptive Statistics of Sample

Variable	Mean (n = 19)	SD	Range
Age at Diagnosis (years)	5.19	2.60	1.50 – 10.83
Age at End of Treatment (years)	8.04	2.41	4.75 – 12.67
Age at Testing (years)	14.75	3.24	10.00 – 21.83
Years out of Treatment	6.71	2.65	2.50 – 11.17

Appendix D

Ethnic Makeup of the Sample

Table 3

Ethnic Makeup of Sample

Ethnicity	*N*	Percentage of Sample
Caucasian	15	79
Latino	4	21

Appendix E

Descriptive Statistics of Working Memory Composite Scores

Table 4

Descriptive Statistics of Working Memory Composite Scores

Variable	Mean (n = 19)	SD
WMC[a]	-0.479	0.7627
VWMC[b]	-0.1158	0.9023
NVWMC[c]	0.1584	0.7646

[a]Working Memory Composite
[b]Verbal Working Memory Composite
[c]Nonverbal Working Memory Composite

Appendix F

Descriptive Statistics by Gender

Table 5

Descriptive Statistics by Gender

	Males n = 14		Females n = 5	
Variable	Mean (SD)	Range	Mean (SD)	Range
WMC	-0.0086 (0.8498)	-1.11 –1.67	-0.1580 (0.49962)	-0.56 – 0.44
Verbal WMC	-.0139 (1.01109)	-1.17 – 1.65	-0.4010 (0.45092)	-0.84 – 0.17
NVWMC	0.0957 (0.82102)	-1.0 – 1.67	0.3340 (0.62272)	-0.33 – 1.00

Appendix G

Intercorrelations Among All Variables

Table 6

Intercorrelations Among All Variables

Variable	(1)	(2)	(3)	(4)	(5)	(6)
(1) FSIQ	1.00					
(2) WMC	0.646**	1.00				
(3) VWMC	0.621*	0.991**	1.00			
(4) NVWMC/Visual Sequential Memory	0.492*	0.575**	0.462*	1.00		
(5) Digit Span Backward	0.252	0.540*	0.532*	0.329	1.00	
(6) Letters Backward	0.628**	0.976**	0.987**	0.441	0.391	1.00

**** Correlation is significant at the 0.01 level (2-tailed).**

*** Correlation is significant at the 0.05 level (2-tailed.**

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Vita

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